Shahzad G. Raja
Editor

Cardiac Surgery

A Complete Guide

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A Complete Guide

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Dedicated to my parents for their love, endless support, encouragement and sacrifices.

Preface

Cardiac Surgery: A Complete Guide provides a succinct and solid overview of the specialty of cardiac surgery. The book predominantly aimed at trainees as well as practicing surgeons presents in a clear and accessible way the most up-to-date knowledge of the entire specialty of cardiac surgery. With an emphasis on key concepts, high-yield information, and international best practice, it concisely covers the breadth of material needed for certification and practice of cardiac surgery. Thanks to the reader-friendly design, featuring an abundance of illustrations, intraoperative photographs, tables as well as information boxes, the book enables the readers to visually grasp and retain difficult concepts. Evidence-based approaches to the management of a range of cardiac surgical conditions will help readers overcome tough clinical challenges and improve patient outcomes.

Cardiac Surgery: A Complete Guide brings together experts from around the world to discuss the full scope of cardiac surgery. It provides essential, up-to-date, need-to-know information about the latest surgical perspectives and approaches to treatment including innovations in minimally invasive surgery and percutaneous devices. Drawing together current knowledge and evidence and examining all aspects of cardiac surgery in one succinct volume, *Cardiac Surgery: A Complete Guide* is the ideal resource for the trainees as well as practicing surgeons enabling them to effectively apply the latest techniques and evidence-based approaches in their day-to-day practice.

A key feature of the book is the section on Review Questions that contains Single Best Answer Questions that will prove to be an invaluable resource for residents preparing for their certification examinations. The breadth of topics covered and detailed answers expand the versatility of this book to a larger audience including doctors preparing for postgraduate exams and other allied healthcare professionals who will be examined in cardiac surgery.

The questions are in line with the most recent developments in clinical guidelines and have been written in accordance with the recent changes in certification examinations. They are designed to provide a comprehensive coverage of the cardiac surgery curriculum and are similar to those that have or will feature in certification examinations. The answers provide detailed explanations as to how the correct answer is reached, followed by a clear discussion of how the incorrect answers are ruled out and supplementary information about other important aspects of each question. The answers are designed to allow the reader to further enhance their clinical knowledge, understanding, and single best answer technique, thus making this book an excellent aid for exam preparation.

I would like to thank all the contributors who have produced excellent chapters and made this collaborative venture worthwhile. Last but not least, my special thanks to the Springer Nature team—Grant Weston, Leo Johnson, Rajeswari Balachandran, and Swathi Chandersekar—for managing the project with courtesy and patience.

London, UK
2020

Shahzad G. Raja

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Part I

Perioperative Care and Cardiopulmonary Bypass

Cardiac Catheterization

1

Konstantinos Kalogeras and Vasileios F. Panoulas

High Yield Facts

- Selective coronary angiography was first described by Mason Sones in 1958.
- The main goals of invasive coronary angiography are to confirm the presence and nature of coronary artery disease, to assess the location and extent of luminal stenosis and finally, to decide upon the optimal therapeutic approach.
- Coronary angiography is a relatively safe procedure in experienced hands with a mortality rate of 1/1000.
- Ongoing infections, acute kidney injury or failure, severe anemia, active bleeding, previous allergic reaction to contrast and severe electrolyte imbalance are considered relative contraindications.

History of Cardiac Catheterization

Although the first cardiac catheterization in animals was performed by the French physiologist Claude Bernard in 1840s, it was not before 1929 when the first right heart catheterization was done in human by the German doctor Werner Forssmann on himself. Selective coronary angiography was first described by Mason Sones in 1958, while special catheters for coronaries engagement and contrast injection were further developed by Kurt Amplatz and Melvin Judkins in 1967 (Fig. 1.1) [2]. The coronary arteries soon became the most frequently examined vessels, using mainly pre-shaped femoral catheters by Judkins, but also those by Bourassa, Schoonmaker, King, El Gamal and many others. After the establishment of coronary angiography, a new era began in September 1977 when the first coronary angioplasty was achieved by Andreas Gruentzig [3].

Invasive Diagnostic Coronary Angiography

Coronary angiography is an integral part of the workup of patients with heart disease and a key element in the evaluation of patients with coronary artery disease (CAD). The main

Fig. 1.1 Melvin Paul Judkins (1922–1985) with his pre-shaped coronary catheters for femoral access (Reprinted from "The PCR-EAPCI Textbook", chapter: A history of cardiac catheterization, Authors: Michel E. Bertrand, Bernhard Meier [1])

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goals of invasive coronary angiography are to confirm the presence and nature of CAD, to assess the location and extent of luminal stenosis and finally, to decide upon the optimal therapeutic approach. Today, the simple coronary angiography has been further enriched by functional evaluation by means of intracoronary pressure measurements and anatomical evaluation using advanced intracoronary imaging modalities. Although coronary angiography is a relatively safe procedure in experienced hands (mortality rate of 1/1000), it can rarely be potentially harmful [4, 5].

Indications

A coronary angiogram is indicated as an *elective procedure*

- For any patient in whom a diagnosis of CAD is suspected or made on clinical grounds or based on additional non-invasive stress tests for the purpose of confirming the diagnosis as well as for defining the optimal therapeutic strategy.
- As part of the preoperative work-up in patients planned for a major non-cardiac or valvular cardiac surgery.

On an *emergency* basis, all patients presenting with acute ST-elevation myocardial infarction (STEMI) should undergo a coronary angiogram and a percutaneous coronary intervention (PCI) within 90 min from presentation [6].

On a *semi-urgent* basis, coronary angiography is indicated for all patients presenting with non ST elevation acute coronary syndromes (NSTEACS) including unstable angina or non-STEMI (NSTEMI) within a timeframe, defined by risk stratification scores [7].

Ongoing infections, acute kidney injury or failure, severe anemia, active bleeding, previous allergic reaction to contrast and severe electrolyte imbalance are considered relative contraindications. However, each patient should be evaluated separately and analyzed on a risk-benefit basis.

Pre-procedure Preparation

Following history and clinical examination, a written informed consent should be obtained in every patient following a clear and full description of the indication(s), the procedure and the treatment options. A routine recent set of blood samples (within a week), is required to ensure patient safety. From the hematology profile, hemoglobin, white cell and platelets count are important [8] to ensure there is no recent or occult blood loss, no underlying infection or thrombocytopenia. With regards to biochemistry tests, creatinine, urea and liver profile are equally important to ensure absence of kidney or liver injury. Bleeding history and evidence of elevated international normalized ratio (INR) or activated partial thromboplastin time (aPTT) are elements of great importance to ensure patient safety. In patients who are anticoagulated (warfarin, novel oral anticoagulants) and managed with transradial approach, there is increased confidence to do diagnostic angiography without treatment interruption [9, 10]. However, elective percutaneous interventions, including pressure wire measurements, should not be performed in anticoagulated patients as the risk of bleeding complications rises.

A transthoracic echocardiogram [11] prior to any coronary catheterization is essential to identify regional wall motion abnormalities, valvular disease or left ventricular thrombus, information that will guide the decision making during coronary angiography.

There is evidence to support the pre-hydration before administration of contrast medium, particularly in patients at risk of contrast induced nephropathy (CIN). However, the modalities of fluid administration remain uncertain [12]. Patient's hydration status should be assessed prior to the procedure, while the aim is to have the patient euvolemic or even slightly hypervolemic before the angiogram. For most patients 1000 ml of 0.9% saline infused over 6 h is considered sufficient. Although not proven, it is considered reasonable to routinely pre-hydrate all patients regardless of renal function [13, 14].

Technical Aspects of the Procedure

Access

This can be gained through femoral, radial, ulnar, brachial or in rare circumstances, axillary/subclavian artery approach. However, transradial approach has mostly replaced the other techniques, becoming the most popular approach, due to the better hemostasis control, faster patient mobilization and increased patient comfort, while data suggest that it is associated with reduced vascular and bleeding complications alongside reduced mortality, particularly in emergency cases [15, 16]. The Seldinger technique used for access is shown in Fig. 1.2. Subsequently, all catheters can be introduced through the sheath and over a J guidewire to the aortic root, to avoid dissecting the vasculature. Problems that can be encountered in advancing the guidewire include severe arterial tortuosity, stenosis, occlusion or dissection. Such difficulties can be overcome only by understanding the anatomy using peripheral contrast injections and the appropriate use of kit (e.g., hydrophilic wires (e.g., Terumo®) or insertion of long sheaths (45 cm), use of guide rather than diagnostic catheters, use of stiff wires (Amplatz super stiff)), ensuring optimal catheter and/or wire manipulation at all times.

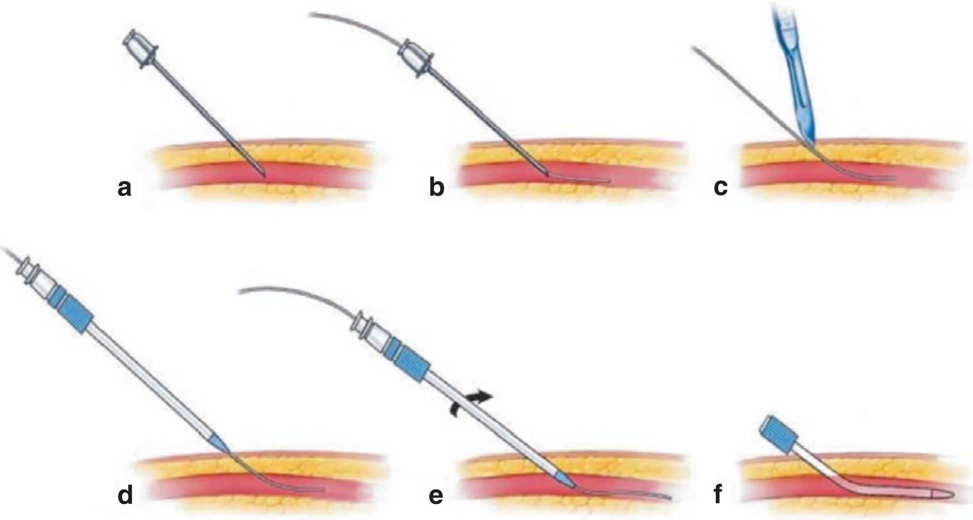

Fig. 1.2 Vascular access for percutaneous insertion of a sheath (**a**) Vessel punctured with the needle until blood back flows. (**b**) A flexible J-tip guidewire advanced through the needle into the vessel lumen. (**c**) The needle removed, and the wire is left in place. The hole around the wire can be enlarged with a scalpel. (**d**) Sheath and dilator placed over the guidewire. (**e**) Sheath and dilator advanced, over the guidewire, into the vessel. (**f**) Dilator and guidewire removed, while sheath is left in the vessel

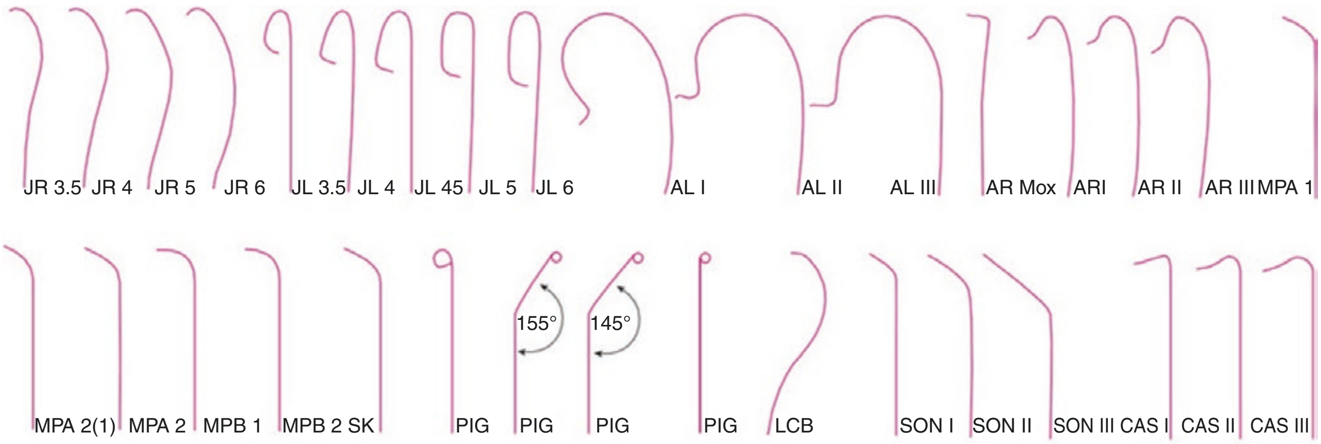

Fig. 1.3 Different catheters available for diagnostic coronary angiography (Reprinted from "The PCR-EAPCI Textbook", chapter: Invasive diagnostic coronary angiography, Authors: Guy R. Heyndrickx, Aaron J. Peace, Chrysafios Girasis, Christoph K. Naber, Christos V. Bourantas, Patrick W. Serruys [17])

Pharmacology

Intra-arterial administration of verapamil or nitrates via the radial sheath is used to limit the occurrence of vascular spasm, an issue not encountered with transfemoral access. Vascular spasm, as well as patient anxiety can be effectively addressed with the use of sedation prior to coronary angiogram. With regards to anticoagulation, for routine transradial diagnostic coronary angiography, an intravenous bolus of 2500–5000 units of unfractionated heparin is adequate for optimal short-term anticoagulation to avoid radial artery occlusion. Finally, it is general practice to administer nitrates (sublingual, intravenous or intracoronary) before starting the coronary angiographic injections to obtain maximal coronary dilatation and prevent potential arterial spasm at the time of catheter manipulation.

Catheter Selection and Manipulation

Improvements in catheter technology have allowed the gradual decrease of diagnostic catheters' size from 8 Fr during the early years of coronary angiography to 6 Fr and even 5 or 4 Fr size catheters. The Judkins left and right (JL/JR) pre-shaped catheters are the most commonly used catheters in the world for engaging the left and the right coronary arteries, respectively. Other pre-shaped catheters (e.g., Amplatz) can be used for injecting both coronary vessels (Fig. 1.3). While initially the same type of preformed catheters were used for the radial approach, more dedicated catheters are now available for radial procedures such as the Kimny (Boston Scientific®), Optitorque Tiger, Jacky and Sarah (Terumo®), Sones (Cordis®) and PaPa (Medtronic®) catheters which allow for engagement of both coronary ostia without need for exchanging catheters.

Angiographic Views

Angiographic views are labelled according to the position of the C-arm image receptor (the flat portion of the C-arm positioned over the patient) in relation to the patient. In the left anterior oblique (LAO) and right anterior oblique [15] the X-ray machine is positioned on the left or right side of the patient respectively, while in the cranial (CRAN) and caudal (CAUD) views the machine is positioned cranially or caudally respectively. When the receptor is in the midline then the term postero-anterior (PA) is used.

Left coronary angiography can be performed by using a wide range of catheters, depending on the approach used (radial, femoral, other) and other anatomic variables including aortic root size, coronary ostia location (high, low, anterior, posterior) and coronary artery take off (superior, horizontal, inferior, Shepherds crook). Before engaging and making injections to the left main or any vessel it is important to recognize that blood is coming freely from the catheter ensuring that the catheter has been purged of air and that a satisfactory arterial pressure trace is obtained. Any reduction in arterial pressure or change in the morphology of the arterial waveform (ventricularization—low diastolic values), should alert the operator that the catheter is obstructing flow, due to either the presence of a true ostial stenosis, or deep catheter engagement (Fig. 1.4). Although individual preferences between operators exist as to which angiographic views and in what order to be obtained, paired orthogonal views are generally required for a correct diagnosis and adequate treatment guidance (Fig. 1.5a, b). Most commonly used views include: RAO caudal, PA caudal, LAO caudal (also termed spider), LAO cranial, PA cranial and RAO cranial.

The right coronary artery (RCA) is intubated in the LAO projection (Fig. 1.6). One of the easy ways to recognize the type of view is the presence (in all cranial vies) or absence (in all caudal views) of the diaphragm. Furthermore to identify whether the projection is LAO or RAO one has to locate the spine which should be seen at the contralateral site of the image in relation to the projection—i.e., on the right of the image in an LAO view.

In 10%–15% of cases an abnormal origin of the RCA complicates the search for the right coronary ostium. A multipurpose, a 3DRC or Williams, an Amplatz right or Amplatz left catheter can be used in these circumstances. For the RCA three views, the LAO, RAO and LAO cranial (20/20) or PA cranial (showing the bifurcation-crux to PDA and PL) are usually sufficient to identify all stenoses. On rare occasions, the left circumflex artery (LCx) can be seen originating from the right coronary sinus (Fig. 1.7).

Left ventricular angiography used to be an essential part of invasive coronary angiogram with pigtail catheters being the first choice. After entering the left ventricle cavity, a correct measurement of the left ventricular end diastolic pressure is the first and most important measurement to evaluate global LV function, while during catheter withdrawal, the pressure gradient across the aortic valve should be measured. Apart from pressure evaluation, left ventriculography offers a lot of information regarding the regional wall motion function of the left ventricle. Usually, it is obtained in two orthogonal views, RAO (30°) and LAO (40°–60°).

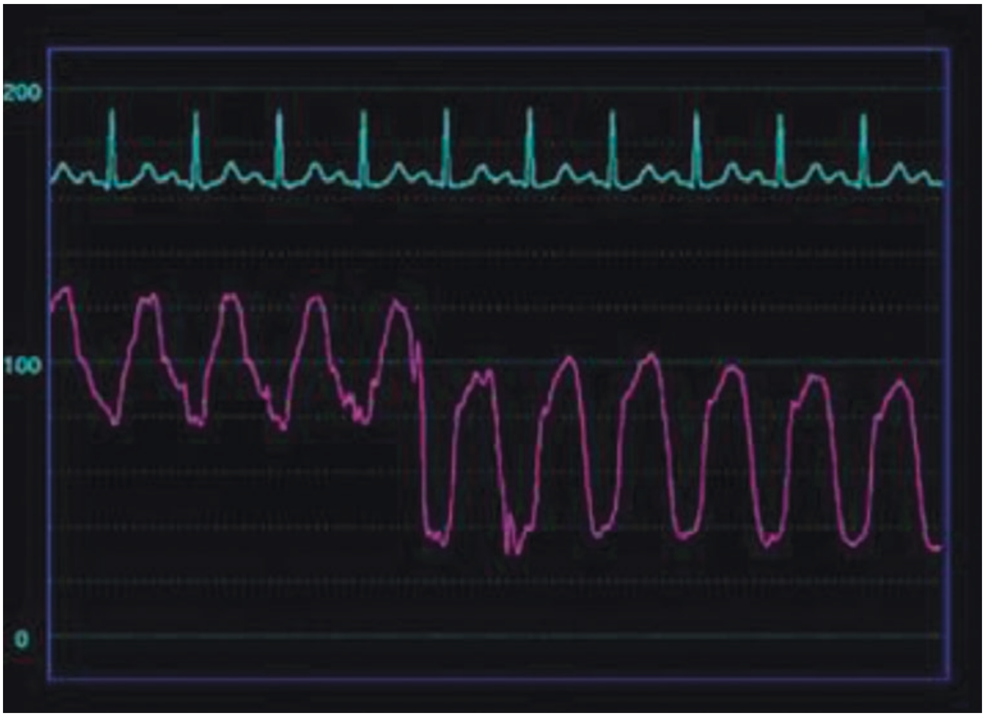

Fig. 1.4 Waveform of pressure ventricularization during coronary ostia engagement due to forward blood flow obstruction

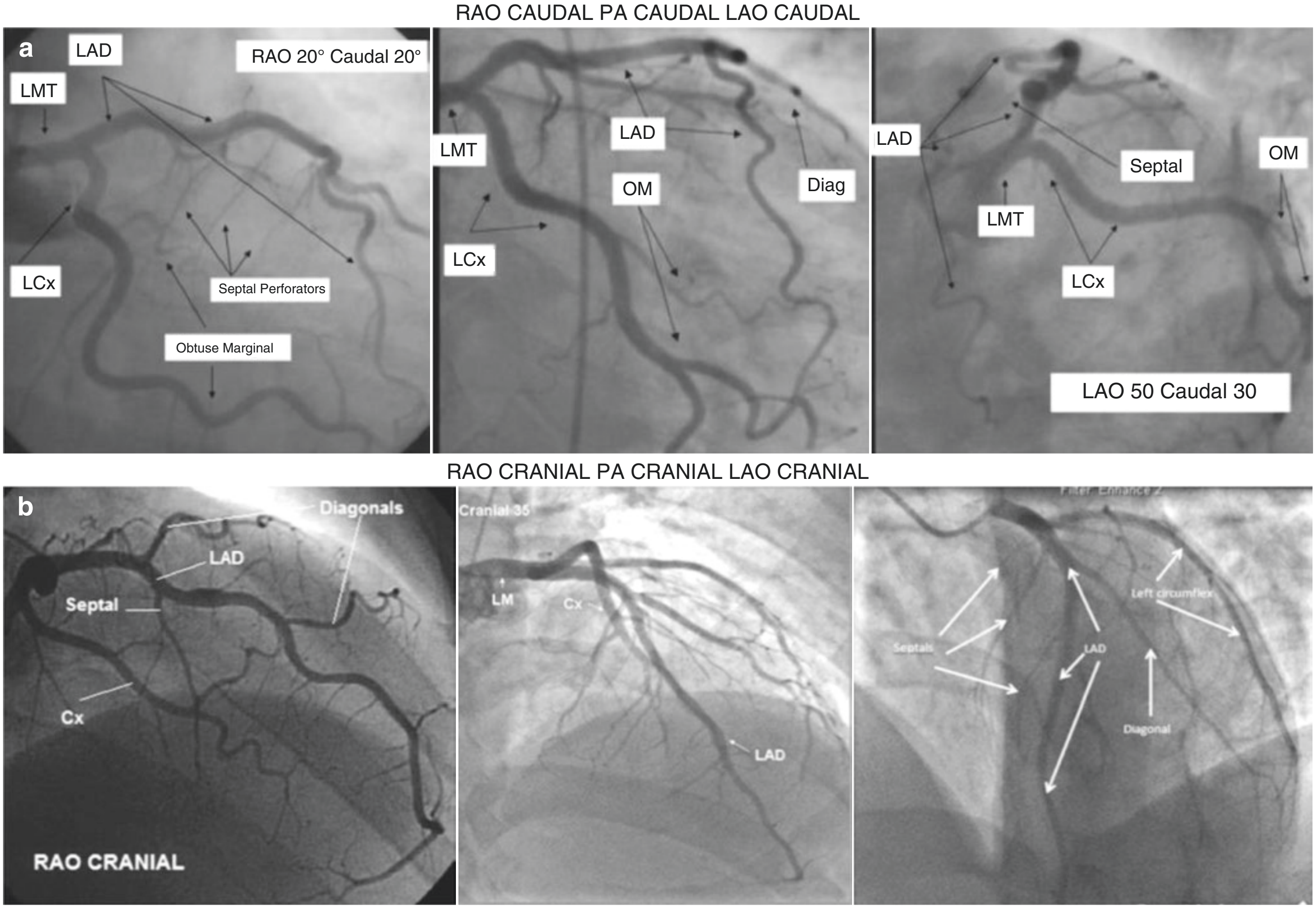
RAO CAUDAL PA CAUDAL LAO CAUDAL
a
LAD
LMT
RAO 20° Caudal 20°
LCx
Septal Perforators
Obtuse Marginal
LMT
LAD
OM
Diag
LCx
LAD
Septal
OM
LMT
LCx
LAO 50 Caudal 30
RAO CRANIAL PA CRANIAL LAO CRANIAL
b
Diagonals
LAD
Septal
Cx
RAO CRANIAL
Cranial 35
LM
Cx
LAD
Septals
LAD
Left circumflex
Diagonal

Fig. 1.5 (**a**) Angiographic caudal views of the left coronary artery system. (**b**) Angiographic cranial views of the left coronary artery system. *LMT* left main stem, *LAD* left anterior descending, *LCX* left Circumflex, *OM* oblique marginal, *Diag* diagonal

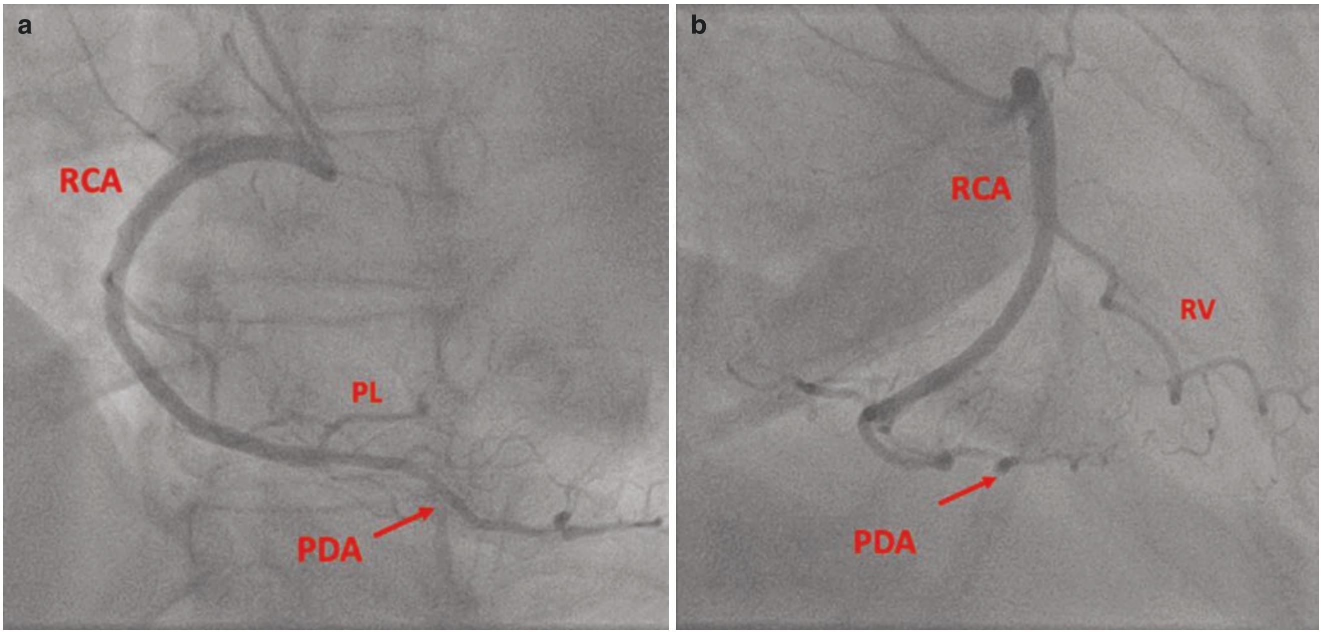
a
RCA
PL
PDA
b
RCA
RV
PDA

Fig. 1.6 Angiographic views of the right coronary artery (RCA). (**a**) Left anterior oblique view (LAO). (**b**) Right anterior oblique. (*RCA* right coronary artery, *PDA* posterior descending artery, *PL* posterolateral branch, *RV* right ventricle branch)

Post-procedure Care

Sheath Removal and Closure Devices

Standard manual compression after sheath removal is usually enough to acquire haemostasis after transfemoral approach diagnostic angiography. However, several vascular closure devices have been introduced to alleviate potential bleeding complications; these can be suture-based (Prostar, Proglide etc.), collagen-based (Angioseal), non-collagen based or clip closure [18, 19]. In case of transradial access, manual compression can often stop the bleeding, while a number of devices have been designed to provide haemostasis (e.g., TR band).

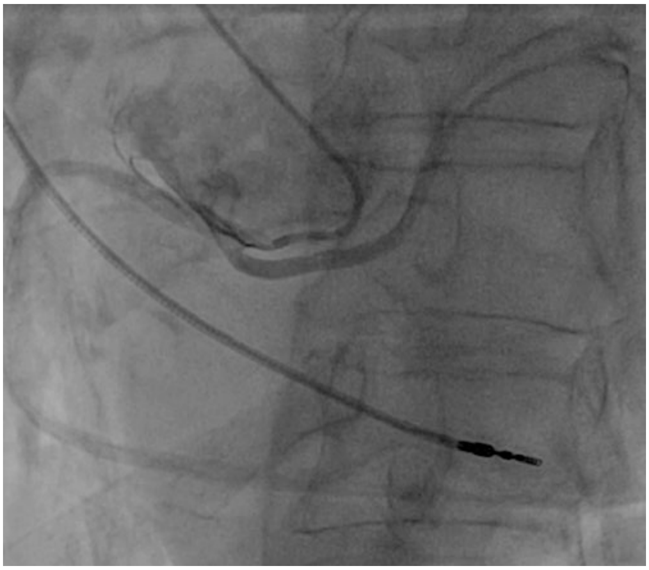

Fig. 1.7 Anomalous origin of the left circumflex artery (LCx) from the right coronary sinus

Coronary Angiogram Analysis

The conventional angiographic classification is based on visual estimation of the diameter reduction of the stenosis compared to a normal segment. The severity classification ranges from low grade stenosis (<49%), to intermediate grade (50–74%), high grade (75–90%), subtotal (91–99%) and total occlusion (100%) [20]. Further parameters required to describe in detail a coronary lesion, are the length of the stenosis, the eccentricity, tortuosity, degree of calcification, and relation to bifurcation. A number of scoring systems have been proposed to describe coronary anatomy, like the ACC/AHA Classification, the Leaman score and the SYNTAX score [21–24].

Examples of coronary lesions are shown in Figs. 1.8–1.11; Fig. 1.8 demonstrates a subtotal occlusion of the ostia of the intermediate and the left circumflex in a primary setting requiring urgent left main trifurcation stenting. In Fig. 1.9 significant mid RCA (a) and mid LCx (b) lesion are shown pre and post PCI. Figure 1.10 shows examples of LMS disease, distal (a) or diffuse/body (b). Finally, in Fig. 1.11 a tight proximal LAD lesion is shown pre- and post-PCI.

Complications

Coronary angiography is not harmless and carries a certain mortality and morbidity risk. The frequency of serious complications, such as death, myocardial infarction or cerebro-vascular accident with permanent damage, is very low (0.1–0.2%) and is usually attributed to high risk patients. Access site complications, including pseudoaneurysms or hematomas requiring blood transfusions, can occur mainly in case of transfemoral access with an incidence of 2–5%.

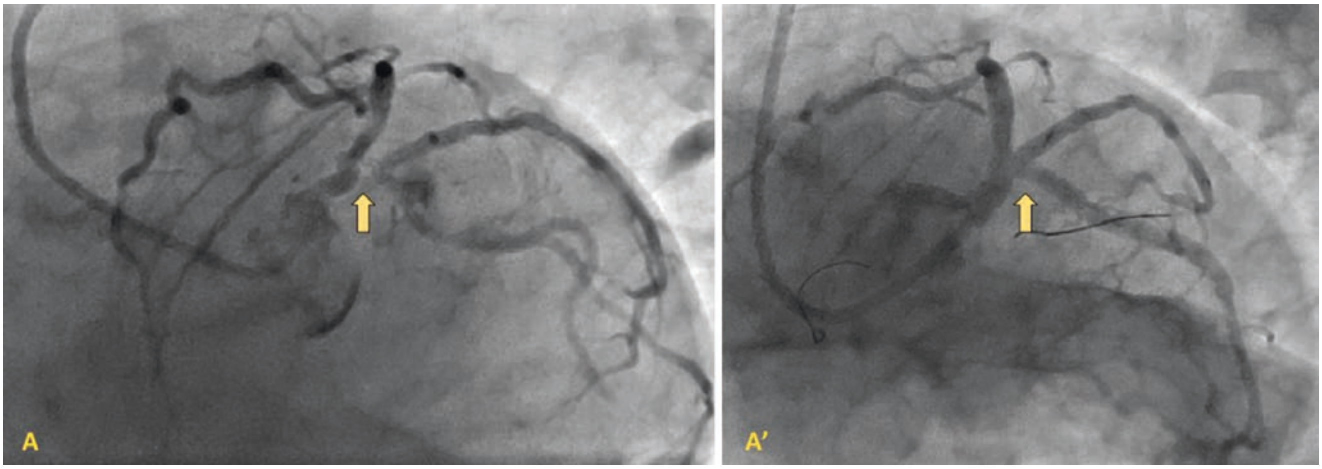

Fig. 1.8 Subtotal occlusion of ostial intermediate and LCx involving the left main stem (LMS) before (**a**) and after (**a′**) primary PCI of the trifurcation

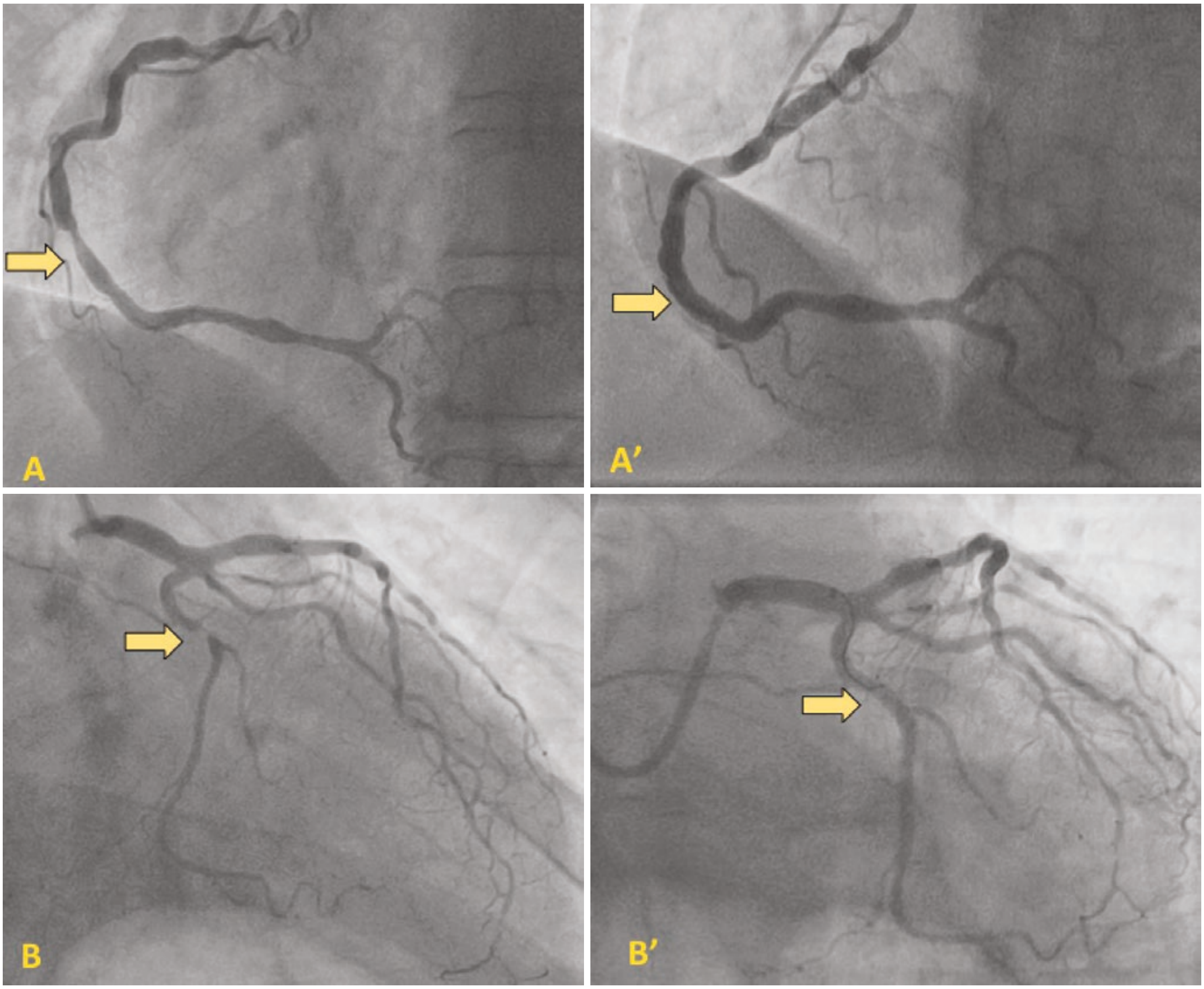

Fig. 1.9 Significant mid right coronary artery (RCA) lesion (**a**) treated with percutaneous coronary intervention (PCI) (**a′**). Tight mid LCx lesion (**b**) also treated with PCI (**b′**)

With the newer generation of contrast agents, allergic reactions are becoming less frequent. However, severe reactions, including prolonged hypotension, bronchospasm, laryngeal edema, and severe anaphylactic shock have been reported. Severe hypotension during a coronary angiogram can be caused due to vasovagal reaction, drug reaction, cardiac tamponade, coronary dissection/occlusion/perforation retroperitoneal bleeding or anaphylactic shock. Furthermore, pulmonary edema can occur after contrast and volume loading especially in those patients with an already decreased left ventricular function. Transient myocardial ischemia can be caused by accidental air bubble injection. Finally, severe complications can occur by catheter manipulation or forceful against the wall injections, causing dissection of the aortic root or coronary ostia.

Right Heart Catheterization

Indications

Pulmonary artery catheters (PACs), also called Swan-Ganz catheters, are used for the management of critically ill patients, and for the evaluation of unexplained dyspnoea or suspected pulmonary hypertension. They are particularly helpful in the acute setting in the management of severe cardiogenic shock. In an elective setting, right heart catheterization (RHC) is the cornerstone for the diagnosis and follow up of pulmonary artery hypertension. Furthermore, RHC can be helpful in identifying the severity of other underlying cardiopulmonary diseases (e.g., congenital heart disease, left-to-

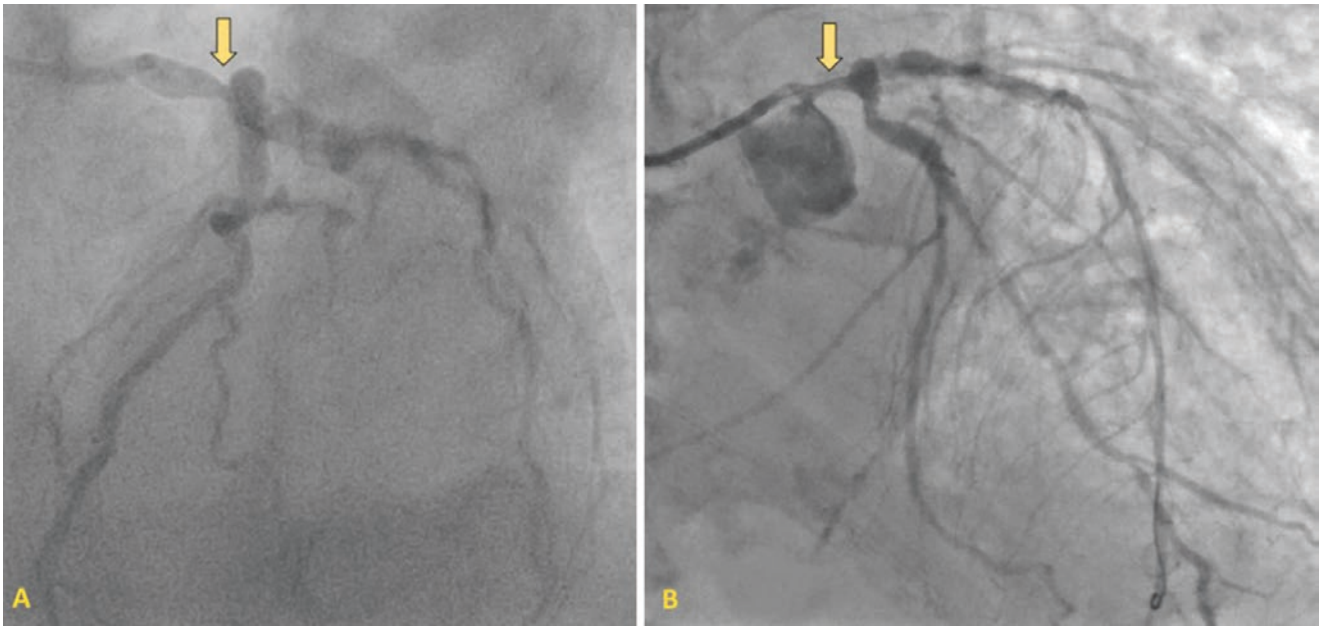

Fig. 1.10 Different patterns of left main stem (LMS) disease. Distal LMS (**a**) versus diffuse calcific body disease (**b**)

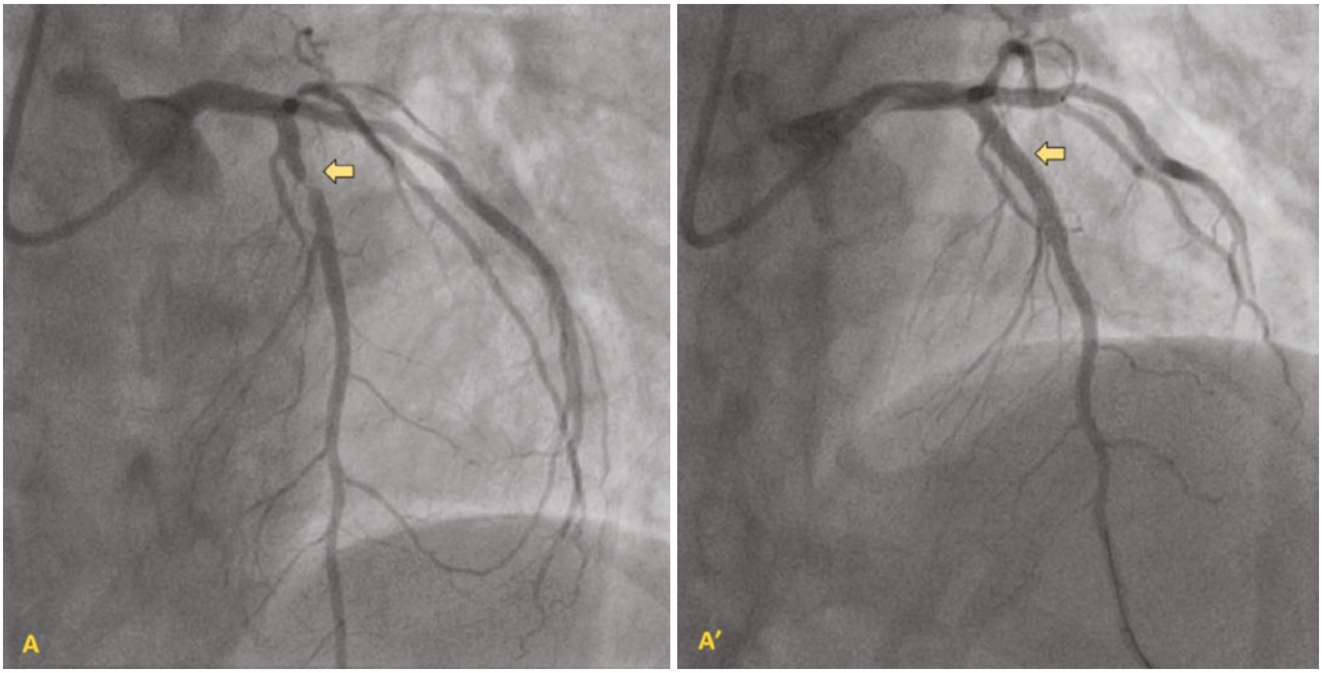

Fig. 1.11 A tight proximal left anterior descending (LAD) artery lesion before (**a**) and after (**a′**) percutaneous coronary intervention

right shunt, severe valvular disease such as mitral valve disease, pulmonary hypertension) prior to corrective or other surgery.

Direct measurements of the following can be obtained from an accurately placed PAC: Central venous pressure (CVP), right-sided intracardiac pressures (right atrium [RA], right ventricle [RV]), pulmonary arterial pressure (PAP), pulmonary capillary wedge pressure (PCWP) and mixed venous oxyhemoglobin saturation (SvO_2).

The PAC can also indirectly measure the following: Cardiac output (CO), cardiac index (CI = CO/body surface area), systemic vascular resistance (SVR = 80 × [mean artery pressure − CVP]/CO), and pulmonary vascular resistance (PVR = 80 × [mean PAP − PCWP]/CO).

Procedure

Access is obtained either from the common femoral vein or the forearm, basilic, cephalic or median cubital vein of the arm. Most commonly the catheters used to perform a RHC are multipurpose and Swan-Ganz (5 Fr or 7 Fr sheath) which has an inflatable balloon on its tip and generally safer to use [11].

Complications

Complications are rare but these can be life threatening including RV/RA chamber perforation followed on by tamponade or distal pulmonary artery perforation (which carries a 40–70% mortality and requires often emergency thoracotomy) [25]. Less sinister complications include access site hematomas, arrhythmias, pulmonary infarction, thromboembolism or stroke—in the presence of patent atrioseptal defect or patent foramen ovale.

Interpreting Haemodynamics

Pressure waveforms are obtained in various locations including the RA, RV and PA and its terminal branches.

Right Atrium

The normal waveforms include:

- a wave: contraction of the atria, x descent is the drop in RA pressure following the contraction
- c wave: represents the closure of the tricuspid valve
- v wave: ventricular systole alongside the passive atrial filling, followed by the y descent which represents the opening of the tricuspid valve

Cannon/giant a waves can be seen in any cause of atrioventricular (AV) dissociation (complete heart block, V-paced rhythm, ventricular tachycardia, AV nodal tachycardia etc.). In atrial fibrillation a-waves are absent [26].

Normal RA pressures range from 0 to 7 mmHg. These can be elevated in

- Conditions that cause downstream pressure elevation (pulmonary hypertension, pulmonary valve stenosis),
- Volume/pressure overload due left to right shunts,
- RV dysfunction (cardiomyopathies including restrictive, infarction)
- Tricuspid valve disease (regurgitation causing tall v-waves – even cv waves, and stenosis cannon a waves)
- External compression (tamponade, constrictive pericarditis).

Right Ventricle

Normal RV systolic pressure varies from 15 to 25 mmHg and normal RV end diastolic pressure (RVEDP) from 3 to 12 mmHg. The RV diastolic wave form consists of early rapid filling (60% of filling), slow filling phase (25% of filling) and an atrial systolic phase (a-wave in RV trace).

RV systolic pressures are elevated when there is increased afterload (e.g., pulmonary hypertension, massive pulmonary embolism, pulmonary stenosis). Elevations in RVEDP occur when RV is failing (longstanding pulmonary hypertension, cardiomyopathies affecting RV, RV infarction), external compression (constriction, tamponade).

Pulmonary Artery

Normal PA systolic pressures range from 15 to 25 mmHg while PA diastolic pressures from 8 to 15 mmHg. Mean PA pressures vary from 10 to 22 mmHg (typically around 16 mmHg). Pulmonary hypertension is defined as a mean PA pressure ≥ 25 mmHg.

The etiology of pulmonary hypertension is split in the following 5 categories:

1. Pulmonary arterial hypertension (e.g., idiopathic, connective tissue disease, congenital heart disease).
2. Left heart disease (e.g., left heart failure, mitral valvular disease).
3. Chronic lung disease and/or hypoxemia (e.g., emphysema, interstitial lung disease).
4. Chronic pulmonary thromboembolism.
5. Multifactorial mechanisms (e.g., sickle cell disease).

Transient elevations in PA can occur in massive/submassive pulmonary embolism, hypoxia.

Pulmonary Capillary Wedge Pressure

The PCWP is an estimate of the left atrial pressure (LA). This is obtained by inflating the balloon tip of the Swan-Ganz catheter in the distal capillary thus creating a static column of blood between the catheter tip and the left atrium [11]. Normal PCWP varies from 6 to 15 mmHg with a mean of 9 mmHg.

Elevations in PCWP pressure occur in any condition that elevates LA or LV pressures like LV systolic and diastolic failure, mitral and aortic valve disease, cardiac tamponade, constrictive or restrictive cardiomyopathies. Low PCWP can be seen in hypovolemia, pulmonary veno-occlusive disease and obstructive shock due to large pulmonary embolism [27, 28].

PCWP (as RA) has a, c and v waves as well as x and y descents. Large a waves can be seen in mitral stenosis, LV systolic or diastolic dysfunction. Large v waves can be seen traditionally in severe mitral regurgitation, but also in diastolic LV dysfunction (caused by longstanding hypertension, hypertrophic cardiomyopathy, myocardial infarction) [29].

Cardiac output (CO) can be measured either using the indicator thermodilution or the Fick method [30]. Cardiac index is derived from CO divided by the body surface area (BSA). Normal values for CI are 2.8–4.2 L/min/m^2. Low CO and CI can be seen in LV failure (systolic or diastolic), RV systolic failure, severe mitral regurgitation, pulmonary hypertension and hypovolemia.

Detection of left to right shunts: in the presence of a shunt blood would naturally flow from the higher pressured left chambers to the right corresponding ones. By sampling all the way from superior venal cava, inferior vena cava, RA (high, mid, low), RV and PA the operator can pick up the location of the step up in the oxygen saturation SaO2 (typically >10% rise) compared to mixed venous SaO2. Mixed venous SaO2 is calculated as (3xSVC + IVC)/4 [31]. The degree of the shunting can then be calculated using the ratio of pulmonary flow (Qp) to systemic flow (Qs) as shown below.

$$\mathrm{Qp} / \mathrm{Qs} = \mathrm{SAO}_2 - \mathrm{SMVO}_2 / \mathrm{SPVO}_2 - \mathrm{SPAO}_2$$

where: SAO$_2$ is arterial (aortic) saturation, SMVO$_2$ is mixed venous saturation, SPVO$_2$ is pulmonary vein saturation, and SPAO$_2$ is pulmonary artery saturation.

Finally, the calculation of systemic and pulmonary vascular resistance can be estimated from CO using the Ohm's law (Resistance = Pressure/Flow):

$$\mathrm{SVR} = 80 \times (\text{mean arterial pressure} - \mathrm{RA}) / \mathrm{CO}$$
$$\mathrm{PVR} = 80 \times (\text{mean PA} \quad \mathrm{PCWP}) / \mathrm{CO}$$

Conclusion

The standard coronary angiography, despite its invasive character and the drawback of relying on a limited number of subjectively selected 2D acquisitions, remains the gold standard method for the evaluation of patients with coronary artery disease. However, several softwares have been developed that permit online co-registration of intravascular imaging, hemodynamic indices and angiographic data. These systems provide representation of coronary angiography, combined with details about lesion morphology and plaque composition, as given by intravascular imaging modalities such as intravascular ultrasound and optical computed tomography [32, 33]. While these approaches have still application mainly in the field of research, the role of standard coronary angiography and right heart catheterization in everyday clinical practice remains fundamental.

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Fractional Flow Reserve

2

Vasileios F. Panoulas

High Yield Facts

- Visual angiographic stenosis assessment is a poor predictor of the functional significance of a stenosis.
- Sensor tipped angioplasty guidewires have been developed and are used to measure pressure and flow across a coronary stenosis in the catheterization laboratory.
- A normal fractional flow reserve (FFR) value is 1, while a positive test is considered when the FFR <0.80.
- Dobutamine stress echocardiography has been shown to correlate well with FFR.
- FFR is superior to intravascular ultrasound
- The most common reason to have a false negative FFR (i.e., a falsely high FFR) is guide catheter pressure damping.
- False positive FFR values (falsely low FFR) are the result of technical failures.

Introduction

Myocardial revascularization with either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) is indicated in the presence of significant ischaemia in one or more coronary territories. In most cases, coronary artery stenoses with greater than 80% diameter reduction on coronary angiography are associated with myocardial ischemia as demonstrated in prior non-invasive testing. However, commonly the lesions encountered in coronary angiograms are intermediate (Fig. 2.1), with luminal stenosis in the range of 40–80% diameter reduction [1, 2]. In this subtype of lesions coronary artery physiologic data, usually coronary artery pressure and flow, can aid decision on the need for revascularization, particularly in individuals without prior non-invasive stress test. Furthermore, visual estimation of stenosis severity has been shown to be highly variable between different operators (inter-observer) but also in repeated assessments (intra-observer) [3]. Visual angiographic stenosis assessment is a poor predictor of the functional significance of a stenosis.

Sensor tipped angioplasty guidewires have been developed and are used to measure pressure and flow across a coronary stenosis in the catheterization laboratory [4, 5]. The use of coronary pressure guidewires is generally safe and typically adds a few minutes to the total procedure time for the assessment of each lesion.

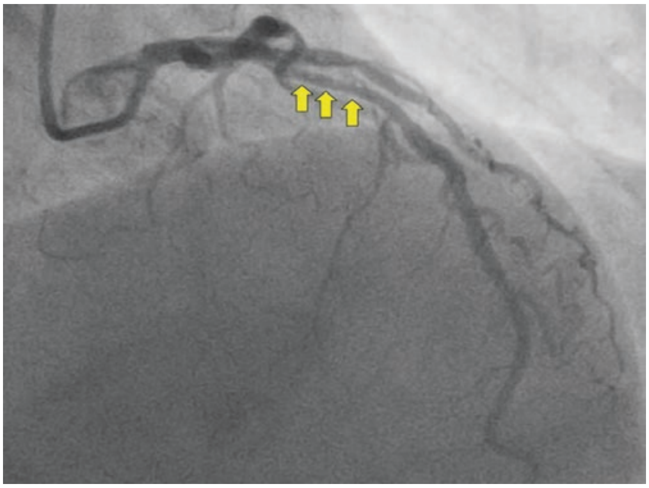

Fig. 2.1 Intermediate lesion on coronary angiography indicated by arrows

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Definitions

Fractional flow reserve (FFR) is the ratio of the maximum achievable blood flow to a myocardial territory in the presence of a stenosis to the maximum achievable flow to the same territory in the absence of the stenosis [6] (Fig. 2.2).

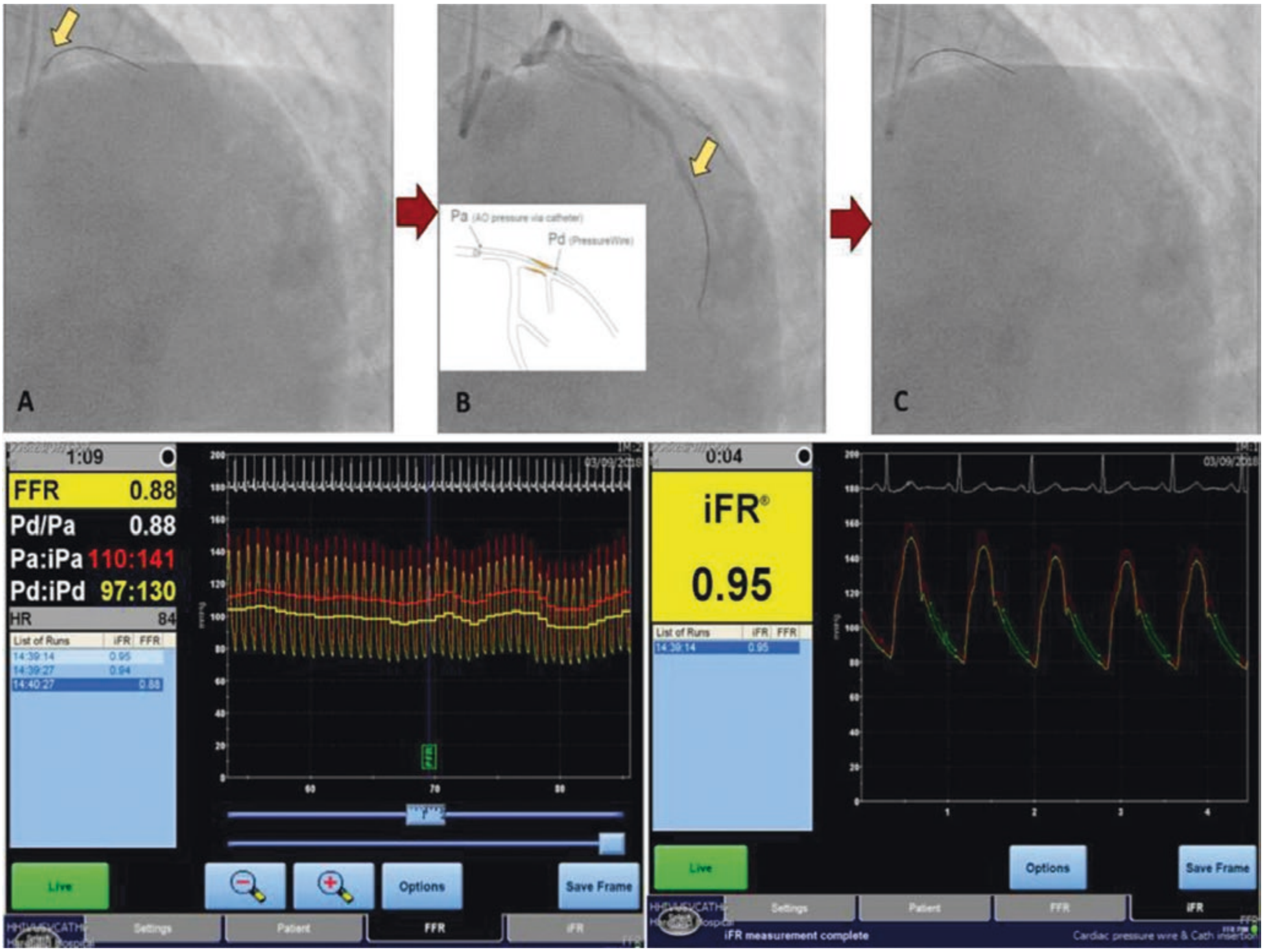
$$FFR = \frac{QS}{QN} = \frac{Pd - Pv \big/ RmyoS}{Pa - Pv \big/ RmyoN}$$

Where

- *Q_S is the maximum achievable flow to the territory supplied by the epicardial vessel with stenosis in question.*
- *Q_N is the maximum achievable flow to the same territory presuming the epicardial vessel is normal.*
- P_d is the pressure measured at the guidewire pressure sensor which should be positioned distal to the lesion in question and
- P_a is the aortic pressure which is the pressure measured at the tip of the guide catheter.
- P_v is the central venous pressure which is much lower than P_a, P_d and close to zero
- *RmyoS* is the myocardial resistance in the territory supplied by the stenosed vessel
- *RmyoN* is the myocardial resistance in the territory supplied by the same vessel with no coronary artery stenoses

If we consider

- The central venous pressure Pv = 0 and
- RmyoS = RmyoN



1:09

FFR 0.88

Pd/Pa 0.88

Pa:iPa 110:141

Pd:iPd 97:130

HR 84

List of Runs	iFR	FFR
14:39:14	0.95	
14:39:27	0.94	
14:40:27		0.88

0:04

iFR® 0.95

List of Runs	iFR	FFR
14:39:14	0.95	

iFR measurement complete

Cardiac pressure wire & Cath insertion

Fig. 2.2 Determination of fractional flow reserve (FFR) and instantaneous wave-free pressure ratio (iFR)

then the equation can be simplified to:

$$FFR = \frac{Pd}{Pa}$$

To obtain accurate FFR measurements, pressures obtained during hyperaemia are required. Maximal blood flow (hyperaemia) is most commonly induced by intravenous (140 mcg/kg/min) or intracoronary adenosine (right coronary artery 50–100 mcg, left coronary artery 100–200 mcg bolus). A normal FFR value is 1, while a positive test is considered when the FFR <0.80.

How Was This Cut-Off Decided?

In a seminal paper by Pijls et al. [7] FFR was compared to exercise testing, thallium scintigraphy, dobutamine stress echocardiography (DSE) and quantitative arteriography in 45 consecutive patients with moderate coronary stenosis and chest pain, prospectively testing the cut-off value of 0.75 [8] to a true gold standard based upon the combination of the three non-invasive tests, all performed within 24 h from the FFR measurement. Using multi-testing sequential Bayesian approach, the sensitivity of FFR in the identification of reversible ischemia was 88%, the specificity 100%, the positive predictive value 100%, and the negative predictive value 88%. In order to avoid not treating an ischemic lesion than treating a non-ischemic lesion, in the FAME [9] and FAME 2 [10] trials a cut-off value of 0.80 was used, demonstrating the prognostic benefits of FFR guided revascularization. In a more recent retrospective study, in an attempt to justify the use of the 0.80 cut-off in clinical practice, Adjedj et al. [11] investigated the outcomes of patients with single lesions in the so called "grey zone" or FFR 0.76–0.80 who were either revascularised or treated with medical therapy alone. Of interest, even though there was no significant difference in overall major adverse cardiovascular events (MACE), there was a trend for higher mortality (p = 0.059) and the combined outcome of myocardial infarction (MI)/death (p = 0.06) in the medical therapy group.

FFR Compared to Other Non-invasive Diagnostic Techniques

DSE has been shown to correlate well with FFR (cut off 0.8) in a study of 62 patients with a single intermediate angiographic lesion with kappa 0.682 and a diagnostic agreement in 87% of patients [12].

Magnetic resonance myocardial perfusion imaging (MRMPI), with intravenous adenosine and a first-pass gadolinium bolus, has been shown to correlate well with FFR (using a cut off at 0.75) in detecting reversible ischemia in a study of 103 patients with stable angina (300 coronary artery segments), MRMPI had a high sensitivity 91%, specificity 94%, positive predictive value 91% and negative predictive value 94% for detecting functionally significant coronary stenosis [13]. In a similar study, of 42 patients who had undergone quantitative stress cardiac magnetic resonance imaging (cMRI) 52 lesions were pressure wired and a cut off of 0.75 was chosen to determine significance. Sensitivity and specificity of cMR to detect haemodynamically significant lesions were 82% and 94% respectively whereas optimum myocardial perfusion reserve (MPR) was 1.58 [14].

Dipyridamole technetium-99 m sestambi (MIBI) single-photon emission computed tomography (SPECT) appears to correlate modestly with FFR in a study of 127 patients (161 coronary lesions) with a 77% diagnostic agreement with FFR and a modest kappa of 0.47 [15].

Single- photon emission computed tomography (PET-CT) myocardial perfusion imaging showed poor correlation with FFR in identifying ischemic territories in patients with multivessel disease, in a study of 67 patients (201 vascular territories) with angiographic 2- or 3-vessel coronary artery disease. The two modalities detected identical ischemic territories in only 42% of patients with kappa of 0.14 (−10 to 0.39) [16].

Adenosine stress computed tomography myocardial perfusion imaging (CTP) showed a moderate correlation with FFR in a study of 42 patients (126 vessels) with at least one >50% angiographic stenosis [17]. CTP achieved 76% diagnostic accuracy in ischaemic lesions and 84% in non-ischaemic territories (Table 2.1).

Table 2.1 Diagnostic indices of non-invasive modalities using FFR as gold standard

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
DSE [12]	60	87.5	100	83.8
Stress cMRI [13]	91	94	91	94
PET-CT [16]	76	38	66	50
CT perfusion [17]	76	84	82	79
MIBI [15]	83	66		

DSE dobutamine stress echocardiography, *cMRI* cardiac magnetic resonance imaging, *CT* computed tomography, *MIBI* dipyridamole technetium-99m sestambi, *NPV* negative predictive value, *PET-CT* Single- photon emission computed tomography, *PPV* positive predictive value

Limitations of Pressure Wire Measurements

The most common reason to have a false negative FFR (i.e., a falsely high FFR) is guide catheter pressure damping (preventing flow into the vessel), failure to induce hyperaemia (wrong concentration, poor intravenous infusion), or acute coronary syndrome with an impaired myocardial bed acutely that then improves over time.

False positive FFR values (falsely low FFR) are the result of technical failures due to inaccurate calibrations, guidewire signal drift downward, or aortic pressure drift upward.

In addition to obstructive focal lesions, flow to the myocardium can be impaired by the presence of diffuse atherosclerotic disease or microcirculatory dysfunction. Other measurements of coronary flow, such as the coronary flow reserve and the index of microcirculatory resistance, have been evaluated as tools for assessing the microcirculation [18]. The role of these measures in clinical practice has not been established.

Intravascular Ultrasound and FFR

Intravascular ultrasound (IVUS), a standard for intravascular anatomic information, has attempted to establish a physiologic correlation to anatomic dimensions. In a prospective registry of 350 patients with 367 intermediate coronary lesions (40–80% by angiography), anatomic measurements by IVUS showed only a moderate correlation with FFR values [19]. The cross-sectional lumen area (i.e., minimal luminal area or MLA) measured by these techniques has been proposed as a surrogate measurement of the functional significance of a given stenosis, however the correlation with FFR has been only moderate. Overall an MLA < 3.07 mm^2 (64.0% sensitivity, 64.9% specificity, AUC = 0.65) was the best threshold value for identifying FFR < 0.8. The accuracy improved when reference vessel-specific analyses were performed. An MLA < 2.4 mm^2 (AUC = 0.66) was best for reference vessel diameters<3.0 mm, an MLA < 2.7 mm^2 (AUC = 0.71) for reference vessel diameters of 3.0–3.5 mm, and an MLA < 3.6 mm^2 (AUC = 0.68) for reference vessel diameters>3.5 mm. FFR correlated with plaque burden ($r = -0.220$, $p < 0.001$) but not with other plaque morphology.

Assessing Left Main Stem Stenosis Using FFR

The left main stem (LMS) stenosis is among the most difficult lesions to interpret angiographically and among the most critical of clinical presentations. LMS stenosis may involve the aortic-ostial junction, mid-body, or distal segments, which may involve the left anterior descending (LAD)/circumflex ostia. When assessing ostial LMS narrowing by fractional flow reserve (FFR) , care is needed to avoid guide catheter damping by disengaging the guide from the ostium and using intravenous adenosine to achieve consistent hyperaemia. In case of a distal narrowing of the LMS, this procedure may be performed twice, once with the pressure wire in the LAD artery and then again in the circumflex artery.

Numerous studies support FFR for assessment of LMS stenoses. In the largest study [20], five-year outcomes were examined in 213 patients with an angiographically equivocal LMS stenosis in whom revascularization decisions were guided by FFR. When FFR was ≥0.80, patients were treated medically or another stenosis was treated by coronary angioplasty (nonsurgical group; n = 138). When FFR was <0.80, CABG was performed (surgical group; n = 75). The five-year survival and event-free survival rates were similar with 90 and 74% in the nonsurgical (FFR ≥0.80) group and 85 and 82% in the surgical (FFR <0.80) group (p = 0.48). Of note only 23% of patients with LMS >50% diameter stenosis had a hemodynamically significant FFR.

FFR in LMS lesions with downstream disease (e.g., LAD lesions) requires an understanding of serial lesions and how they affect one another. The myocardial bed flow for the LMS is the sum of both the LAD and circumflex territories and this flow determines the LMS FFR. In the presence of a significant LAD stenosis, flow in the LAD territory may be reduced, reducing total LMS flow and hence falsely increasing the apparent LMS FFR value. The higher "apparent" LMS FFR is only a concern if either the LAD or circumflex, are severely hemodynamically impaired (FFR of LMS and LAD <0.6) [21]. For serial LMS with downstream LAD disease, when FFR beyond LAD is <0.60, the apparent LMS FFR may be questioned. In this case, IVUS assessment with a threshold of <6.0 mm^2 is recommended.

FFR Use Pre Coronary Artery Bypass Grafting

The issue of whether the use of FFR to evaluate intermediate lesions can improve outcomes in patients referred for CABG has been evaluated in one observational study [22]. Among 627 patients having at least one angiographically intermediate stenosis, 429 had bypass grafts placed based on angiographic findings only, and 198 based on FFR (bypass of a lesion was deferred if the FFR was >0.80). At 3 years, major adverse cardiovascular events (a composite of overall death, MI, and target vessel revascularization) were similar between the two groups (12% versus 11%; HR 1.03, 95% CI 0.67–1.69). The rate of angina was significantly lower in the FFR-guided group (31% versus 47%), despite fewer venous grafts being placed.

While the surgical practice of grafting all vessels with angiographic stenosis of >50% has been a long-standing standard, CABG of vessels with haemodynamically non-significant stenosis has a higher rate of graft closure compared with those vessels with haemodynamically significant stenosis [23]. This was shown in 525 lesions in 153 patients referred for bypass surgery. FFR was performed in all lesions to be grafted, with the surgeon blinded to the results. Repeat angiogram performed one year after CABG showed that 21.4% of grafts on functionally non-significant lesions (FFR >0.75) were occluded, compared with 8.9% of grafts on vessels with FFR <0.75.

Main Outcome Studies with FFR

DEFER Trial [24]

In 325 patients scheduled for PCI of an intermediate stenosis, FFR was measured just before the planned intervention. If FFR was ≥0.75, patients were randomly assigned to deferral (Defer group; n = 91) or performance (Perform group; n = 90) of PCI. If FFR was <0.75, PCI was performed as planned (Reference group; n = 144). After 15 years of clinical follow up the rate of death was not different between the three groups: 33.0% in the Defer group, 31.1% in the Perform group, and 36.1% in the Reference group (Defer vs. Perform, RR 1.06, 95% CI: 0.69–1.62, P = 0.79). The rate of myocardial infarction was significantly lower in the Defer group (2.2%) compared with the Perform group (10.0%) [RR 0.22, 95% CI: 0.05–0.99, P = 0.03].

FAME Trial [9]

In the FAME study, 1005 patients with multivessel coronary artery disease were randomly assigned to undergo PCI with implantation of drug-eluting stents guided by angiography alone or guided by FFR measurements in addition to angiography. The primary end point was the rate of death, nonfatal MI, and repeat revascularization at 1 year. The 1-year event rate was 18.3% (91 patients) in the angiography group and 13.2% (67 patients) in the FFR group (P = 0.02). All-cause mortality at 1 year was 3.0% (15 deaths, 10 of which had cardiac causes) in the angiography group and 1.8% (9 deaths, 7 of which had cardiac causes) in the FFR group (P = 0.19). MI occurred in 43 patients (8.7%) in the angiography group and in 29 (5.7%) in the FFR group (P = 0.07). Repeat revascularization occurred in 47 patients (9.5%) in the angiography group and 33 (6.5%) in the FFR group, p = 0.08. At 5-years major adverse cardiac events occurred in 31% of patients (154 of 496) in the angiography-guided group versus 28% (143 of 509 patients) in the FFR-guided group (relative risk 0·91, 95% CI 0·75–1·10; p = 0·31) [25].

FAME 2 Trial [10]

In 1220 stable angina patients with angiographically significant stenosis, those in whom at least one stenosis was hemodynamically significant (FFR ≤0.80) were randomly assigned to FFR-guided PCI plus medical therapy or to medical therapy alone. Patients in whom all stenoses had an FFR of more than 0.80 received medical therapy and were entered into a registry. The primary end point was a composite of death, MI, or urgent revascularization. A total of 888 patients underwent randomization (447 patients in the PCI group and 441 in the medical-therapy group). At 5 years, the rate of the primary end point was lower in the PCI group than in the medical-therapy group (13.9% vs. 27.0%; hazard ratio, 0.46; 95% confidence interval [CI], 0.34–0.63; P < 0.001) [26]. The difference was driven by urgent revascularizations, which occurred in 6.3% of the patients in the PCI group as compared with 21.1% of those in the medical-therapy group (hazard ratio, 0.27; 95% CI, 0.18–0.41). There were no significant differences between the PCI group and the medical-therapy group in the rates of death (5.1% and 5.2%, respectively; hazard ratio, 0.98; 95% CI, 0.55–1.75) or MI (8.1% and 12.0%; hazard ratio, 0.66; 95% CI, 0.43–1.00) [26].

COMPARE ACUTE Trial [27]

In this study 885 patients with ST elevation MI and multivessel disease who had undergone primary PCI of an infarct-related coronary artery were randomly assigned in a 1:2 ratio to undergo complete revascularization of non–infarct-related coronary arteries guided by fractional flow reserve (FFR) (295 patients) or to undergo no revascularization of non–infarct-related coronary arteries (590 patients). The FFR procedure was performed in both groups, but in the latter group, both the patients and their cardiologist were unaware of the findings on FFR. The primary end point was a composite of death from any cause, nonfatal MI, revascularization, and cerebrovascular events at 12 months. The primary outcome occurred in 8% of patients in the complete-revascularization group and 21% of patients in the infarct-artery-only group that did not receive complete revascularization (HR, 0.35; 95%CI, 0.22 to 0.55; P < 0.001). Death occurred in 4 patients in the complete-revascularization group and in 10 patients in the infarct-artery-only group (1.4% vs. 1.7%) (HR, 0.80; 95%CI, 0.25–2.56), MI in 7 and 28 patients, respectively (2.4% vs. 4.7%) (HR, 0.50; 95% CI, 0.22–1.13), revascularization in 18 and 103 patients (6.1% vs. 17.5%) (HR, 0.32; 95%CI, 0.20–0.54), and cerebrovascular events in 0 and 4 patients (0 vs. 0.7%) [27].

Instantaneous Wave-Free Pressure Ratio (iFR)

An adenosine-independent, resting pressure-derived index of coronary stenosis severity has been developed and tested as a substitute for FFR. Using wave intensity analysis [28], it was determined that the period of diastole in which equilibration or balance between pressure waves from the aorta and distal microcirculatory reflection was a "wave-free period" led to minimal and constant coronary resistance. Pd/Pa during the wave-free period (75% into diastole ending 5 ms before the R wave) is called the instantaneous wave-free pressure ratio (iFR) (Fig. 2.2).

It was demonstrated that at iFR cut off-points of >0.93 or <0.86, there was a strong correlation with normal and abnormal FFR values respectively (using 0.80 as an FFR cut point). In the ADVISE II study [29], iFR was compared to FFR in 690 intermediate stenoses. Compared to FFR (using the 0.80 cut off point), iFR cut-off of 0.89 correctly classified 83% of stenoses. iFR correctly classified those stenoses outside the 0.85–0.94 iFR "gray zone" with 92% agreement.

Two large randomized, non-inferiority trials in low-risk patients have evaluated clinical outcomes in patients with stable or unstable disease who had one or more coronary artery lesions for which physiologic assessment prior to revascularization was indicated; In the iFR SWEDEHEART study, 2037 patients were randomly assigned to iFR (cut off 0.89) or FFR (cut off 0.8) [30]. The primary end point (all cause death from, nonfatal MI, or unplanned revascularization within 12 months) occurred with equal frequency (6.7% versus 6.1%; difference in event rates, 0.7 percentage points, 95% CI −1.5 to 2.8; HR 1.12, 95% CI 0.79–1.58). In the DEFINE-FLAIR trial, 2492 patients were randomly assigned to iFR or FFR [31]. At one year, the primary end point, a composite of death from any cause, nonfatal MI, or unplanned revascularization, occurred with equal frequency (6.8% versus 7.0%; difference in risk, −0.2 percentage points; 95%CI, −2.3 to 1.8; $P < 0.001$ for noninferiority; HR, 0.95; 95% CI, 0.68–1.33; $P = 0.78$).

Conclusions

FFR has become the clinical standard for the invasive physiologic assessment of the hemodynamic significance of intermediate stenoses. FFR is superior to intravascular ultrasound and in many cases to noninvasive stress radionuclide myocardial perfusion imaging. For intermediate stenoses where there is a question of whether revascularization should be carried out, with no prior noninvasive physiologic data to guide decision making, FFR should always be measured before the decision to revascularize.

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Echocardiography

3

Shelley Rahman Haley

High Yield Facts

- Echocardiography is the most widely-practiced noninvasive imaging modality and uses ultrasound to build up a detailed anatomical and physiological picture of the heart and great vessels.
- Echocardiography is widely-available, repeatable, reproducible, very low-risk, virtually painless and relatively cheap.
- Different modalities of imaging within the technique allow the identification and accurate assessment of global and regional ventricular systolic and diastolic dysfunction, myocardial viability and ischemia, stenotic and regurgitant valve lesions, pericardial disease and intracardiac masses.
- Data accumulated over almost five decades of practice means that information obtained by echocardiography predicts outcomes of surgical procedures including mitral valve repair, aortic valve replacement, myocardial revascularization and left ventricular assist device implantation.

Introduction

Echocardiography uses ultrasound to build up images of the heart and great vessels. In cardiothoracic surgery in developed economies, it is the most widely-practiced and highest-volume non-invasive diagnostic imaging test performed. The proven utility of the technique along with its low risk-profile mean that it is the cornerstone of cardiac imaging. Entire textbooks are devoted to single modalities of echocardiography, and the interested reader is directed to the bibliography at the end of this chapter. However, this chapter is intended to provide a brief and focused survey of the technique as it applies to the cardiothoracic surgical patient. A brief section on ultrasound theory is included, containing only the facts deemed to be essential for a basic understanding of the way various measurements are made and parameters calculated. Some formulae are also included in the text where it is felt that this facilitates understanding.

Essential Ultrasound Theory for Echocardiography

The ultrasound used in echocardiography is produced by passing electric current through a piezoelectric crystal, causing it to vibrate at frequencies of 2–7 MHz. The ultrasound waves pass through the tissues of the thorax, and are scattered, attenuated or reflected particularly at tissue interfaces. The reflected signals deform the piezoelectric crystal and generate tiny electric currents which are used to build up a detailed picture of the structure of the heart. The simultaneous recording of the patient's surface ECG allows the images to be gated, transforming them into the real-time cines with which surgeons are most familiar (Fig. 3.1). Doppler echocardiography utilizes the physics of the Doppler frequency shift to allow calculation of the speed of motion of blood through the heart valves and this in turn allows the calculation of valve area/stenosis, cardiac output and regurgitant volume. The attenuation of ultrasound by body tissues means that image quality is affected by body habitus, and some subjects simply have poor acoustic windows, so image quality can never be guaranteed. Nevertheless, with advances in hardware and software, there are few patients in whom useful information cannot be obtained.

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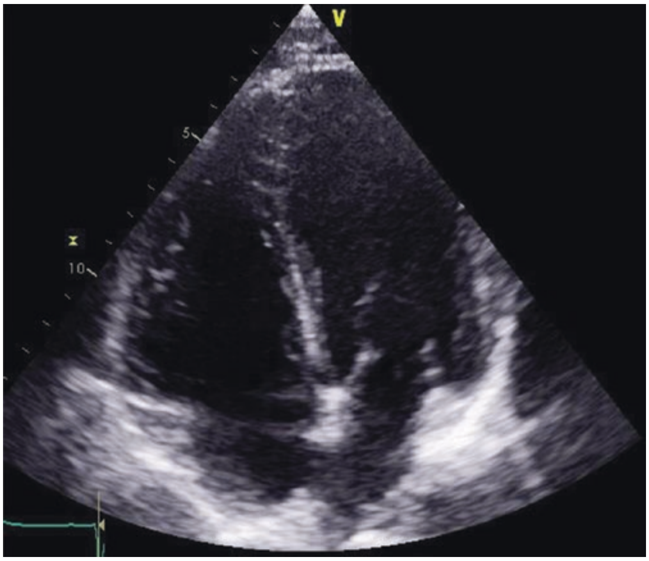

Fig. 3.1 2D 4-chamber view in a patient with a normal heart

Modalities of Echocardiography

In addition to the 2D echo images already mentioned, there are a number of other echo modalities with specific uses and these are summarized in Table 3.1.

Table 3.1 Modalities of echocardiography and their main uses

Modality of echo	Advantages	Disadvantages	Main uses
2D	Recognizable, moving images	Dependent on acoustic windows and operator	Anatomy and morphology; "eyeballing" function and valve motion
M Mode	Very high temporal resolution	Images harder to interpret for the less experienced observer	Dimensions, accurate timing of motion of structures such as valve leaflets
CW (continuous wave) Doppler	Can be used with 2D and color flow Doppler to measure velocities over a wide range	Not fully steerable so measurements may be less accurate if correct angle cannot be obtained	Measuring velocities across stenotic and regurgitant valves
PW (pulsed wave) Doppler	Sample volume means able to localize velocities at a specific point in the heart	Can only be used to measure velocities up to 2 m/s	Measuring filling parameters, LVOT /RVOT velocity, pulmonary and hepatic venous flow
"Standalone" CW Doppler	Highly steerable allowing accurate measurement of velocities at tricky angles	The operator cannot see the 2D image simultaneously, so harder to use and requires more experience	Valve lesions, accurate assessment of aortic stenosis, separating out complex overlapping velocity traces

2D two dimensional, *CW* continuous wave, *LVOT* left ventricular outflow tract, *RVOT* right ventricular outflow tract

Motion-mode (M-mode) has extremely high temporal resolution and is particularly good for situations where an understanding of the relative timing of events is key. An example of this is in the assessment of the hemodynamic significance of a pericardial effusion when the presence of early diastolic collapse of the free wall of the right ventricle is one of the important echo indicators of incipient tamponade [1].

Pulsed-wave (PW) and continuous-wave (CW) Doppler echocardiography are used to assess flow velocity (Fig. 3.2). The former is uses a sample-volume to provide information from a particular selected depth, but is only able to assess relatively low flow velocities (up to approximately 1.8 m/s). This is because the transducer acts as a receiver for the time necessary for the signals to return from the sample volume, after which a further pulse is emitted. This in turn means that there is a limit to the sampling rate, and this limits the maximum velocity able to be detected accurately [1]. Continuous wave Doppler is not limited in this way because the transducer acts as a continuous emitter and receiver of ultrasound. However, this modality is not able to provide range resolution.

Color flow Doppler is used to provide an easy, immediately-appreciable visual assessment of blood flow through the chambers and valves. By convention, in areas of the image where blood is flowing towards the transducer it is coded red and when it is flowing away from the transducer it is coded blue. Although color flow mapping allows the viewer to easily appreciate abnormal flows such as fistulae, septal defects (Fig. 3.3), regurgitant valve lesions and the turbulence associated with stenotic lesions, attempting to quantify the severity of a lesion from the appearance of the color jet alone is fraught with error and should be avoided.

Tissue Doppler imaging (TDI) uses the Doppler principle to assess the motion of myocardium, most commonly at the lateral and septal mitral annulus and the RV free wall. Abnormal TDI is a good way to confirm early myocardial dysfunction and is also particularly useful when assessing diastolic filling (Fig. 3.4) and when differentiating pericardial constriction from restrictive cardiomyopathy—an E' at the lateral annulus of ≥8 cm/s indicates constriction rather than restriction.

Strain imaging by echocardiography measures the extent of myocardial deformation, i.e. the change in myocyte length during systole. Change in length per unit time is *strain rate*. Either global or regional strain or strain rate can be measured and evidence is growing that strain abnormalities are one of

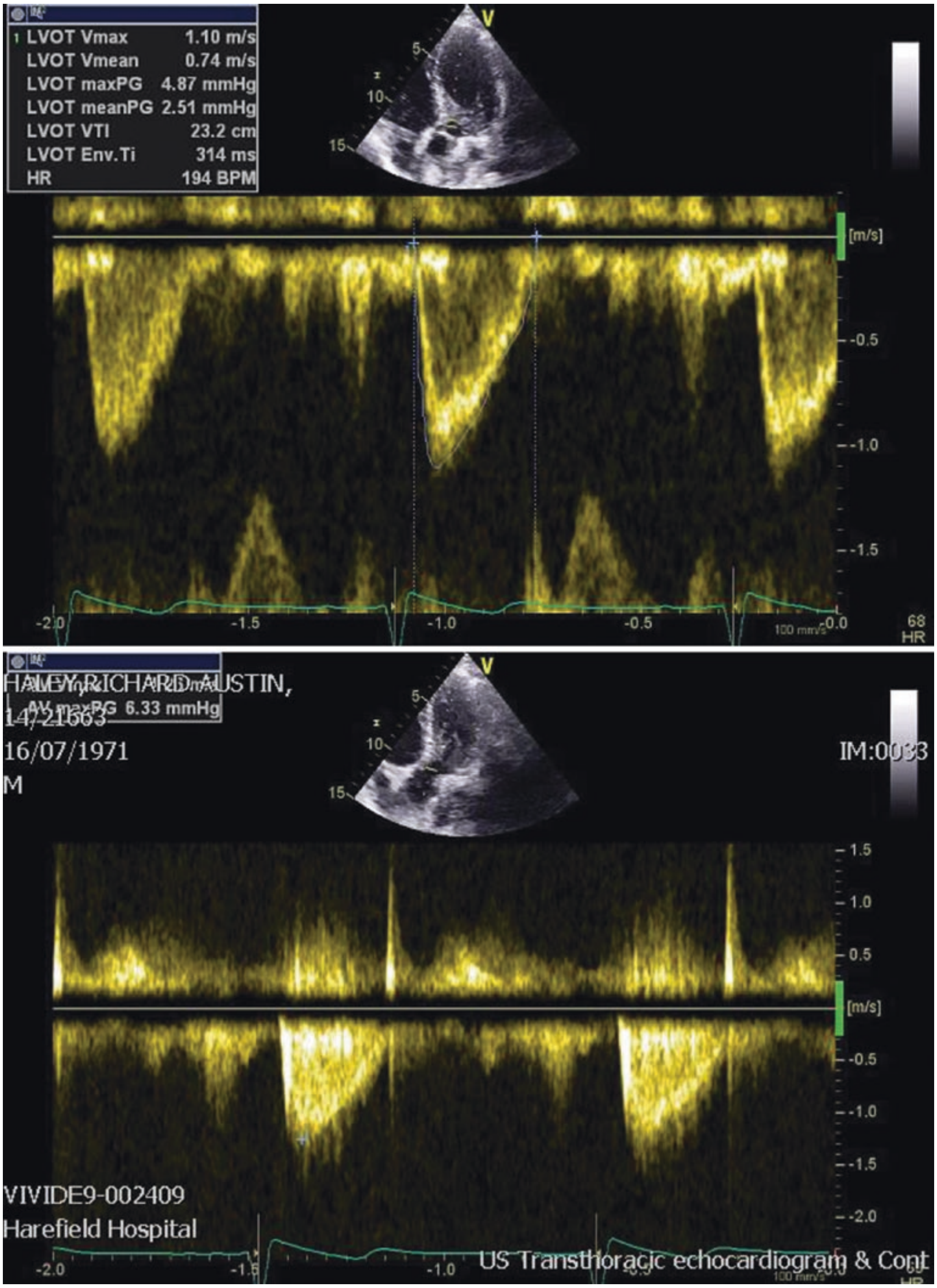
LVOT Vmax 1.10 m/s
LVOT Vmean 0.74 m/s
LVOT maxPG 4.87 mmHg
LVOT meanPG 2.51 mmHg
LVOT VTI 23.2 cm
LVOT Env.Ti 314 ms
HR 194 BPM
[m/s]
-0.5
-1.0
-1.5
-2.0
-1.5
-1.0
-0.5
0.0
68 HR
HALEY, RICHARD AUSTIN,
AV maxPG 6.33 mmHg
16/07/1971
M
IM:0033
1.5
1.0
0.5
[m/s]
-0.5
-1.0
-1.5
-2.0
VIVIDE9-002409
Harefield Hospital
US Transthoracic echocardiogram & Cont

Fig. 3.2 Top panel shows PW Doppler from a normal left ventricular outflow tract; Bottom panel is CW Doppler across a normal aortic valve. Note that PW traces appear "hollowed out". This is because most of the signal is coming from one particular depth—in this case approximately 1 cm below the aortic valve

the earliest detectable signs of subclinical contractile dysfunction. The normal value for global mean longitudinal strain is ≥−19%. Marked reductions in global strain are seen in cardiomyopathies, and in particular in infiltrative cardiomyopathies such as amyloidosis (Fig. 3.5).

Three-dimensional (3D) echocardiography is a relatively new development and although initially very exciting, it has taken some time to find its place in the armamentarium. This was probably due to limitations in probe technology in its early iterations, which limited temporal resolution, especially with color flow Doppler. However, with technological advances, it has become clear that 3D echo has a role to play especially in planning complex surgical procedures such as mitral valve and aortic root repair, in complex congenital heart disease, in the assessment of intracardiac masses including thrombus in the left atrial appendage and in assessing the complications of infective endocarditis [2] (Figs. 3.6 and 3.7).

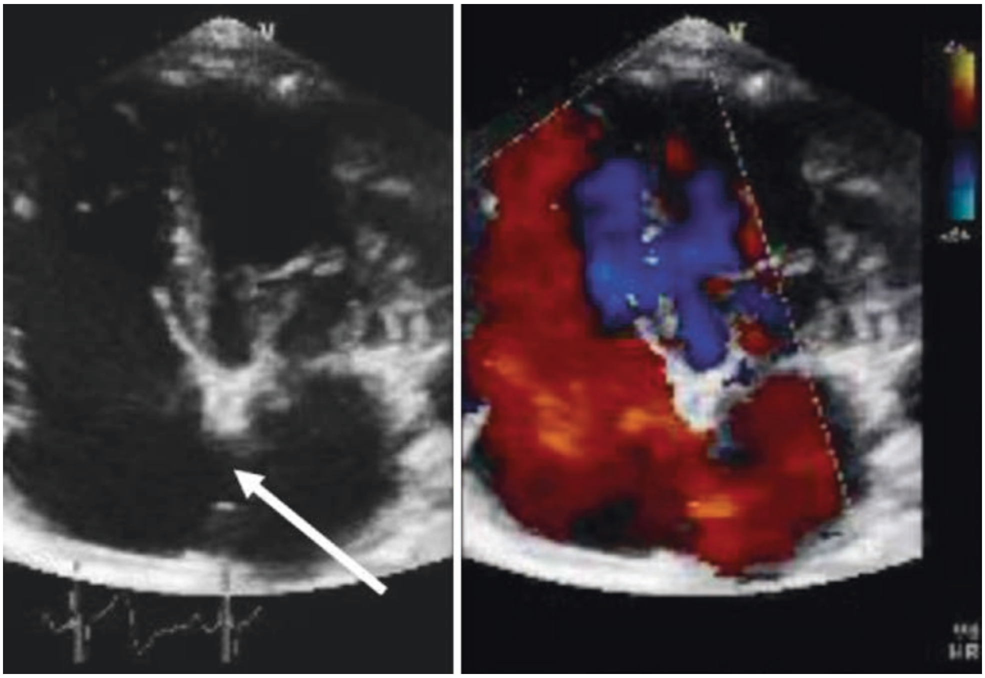

Fig. 3.3 Colour flow Doppler confirming a large secundum atrial septal defect (arrow) in a 6 year-old boy. Red color indicates blood moving towards the transducer, at the apex of the scan sector

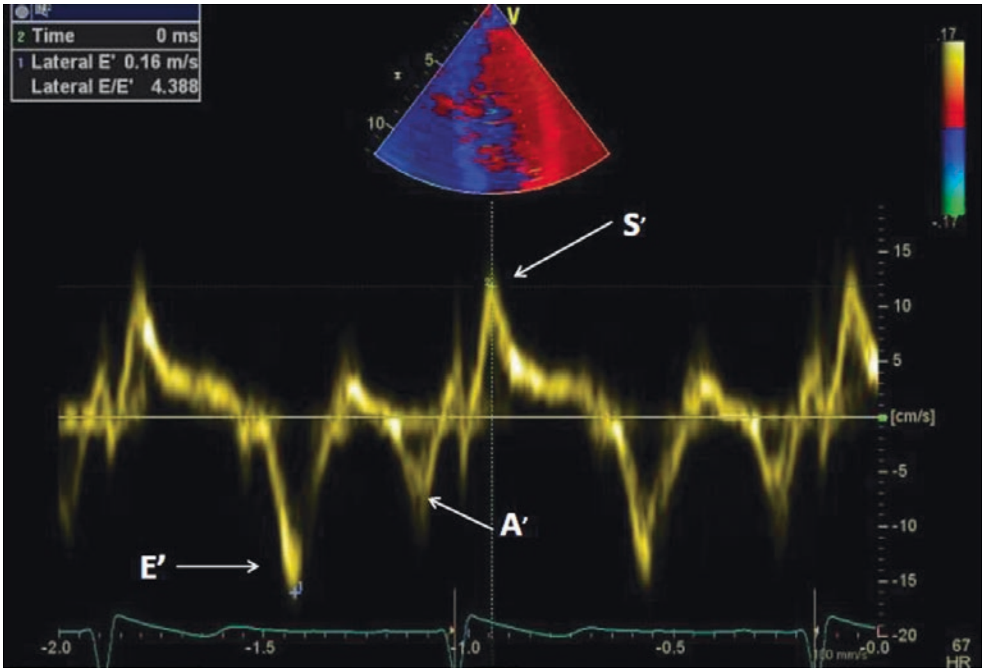

Fig. 3.4 Normal tissue Doppler signals from the lateral mitral annulus. The S′ velocity should be >10 cm/s

Assessment of Myocardial Function

Left Ventricular Systolic Function

The assessment of myocardial systolic contractile function is done indirectly by echocardiography by assessing three parameters; the change in volumes (2D/3D) or dimensions (2D/M-mode) from diastole to systole, indices of contractility such as the rate of rise of pressure with time (dp/dt) and Tei index, and strain. None of these is perfect and all are, to a greater or lesser extent, load-dependent.

Changes in Volumes/Dimensions

The most frequently requested and quoted parameter is the *left ventricular ejection fraction* (LVEF) which is the stroke volume expressed as a proportion of the end-diastolic volume. If end-diastolic and end-systolic dimensions are measured by 2D or M-mode then the *fractional*

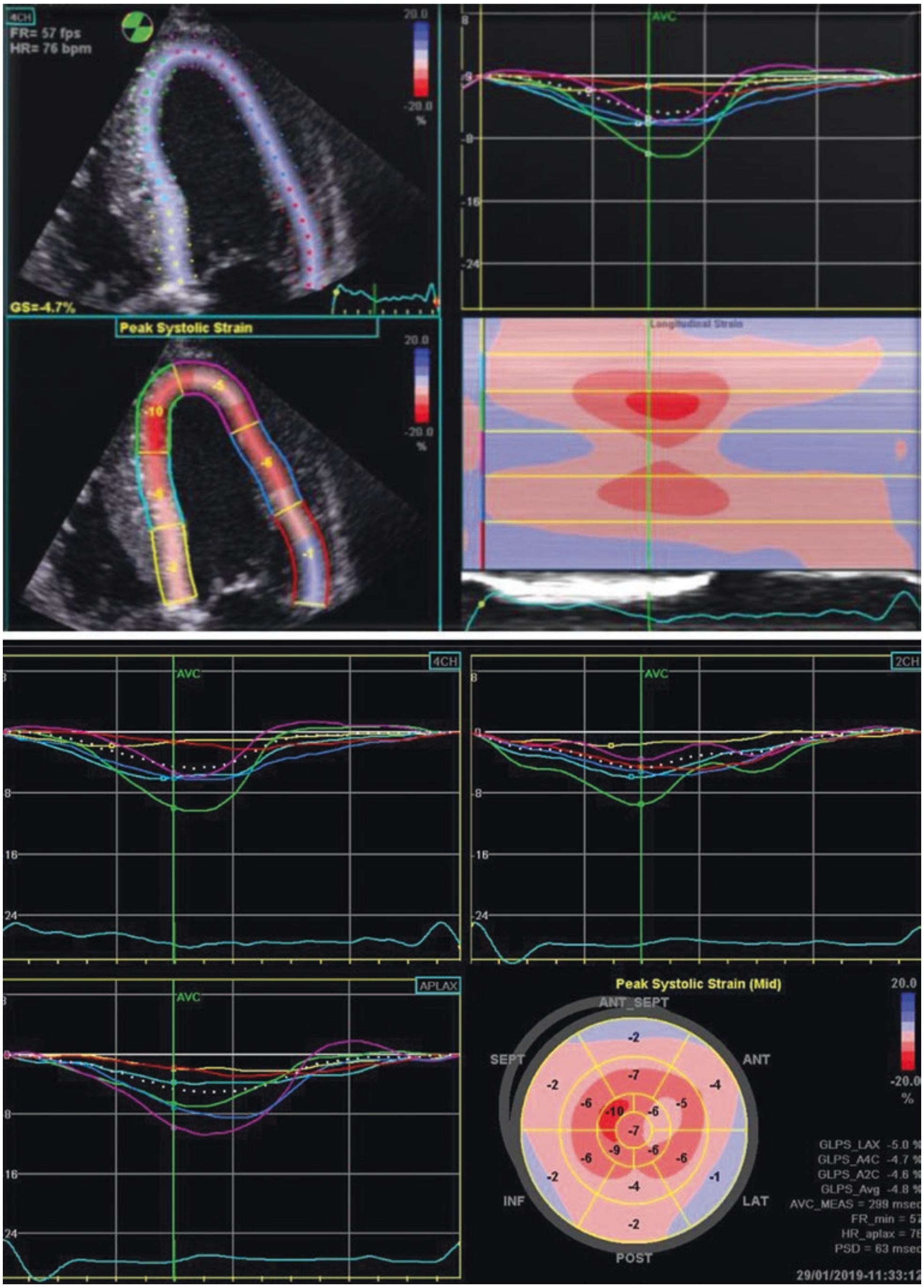
4CH
FR= 57 fps
HR= 76 bpm
20.0
-20.0
%
GS=-4.7%
Peak Systolic Strain
AVC
Longitudinal Strain
8
-8
-16
-24
4CH
2CH
APLAX
Peak Systolic Strain (Mid)
ANT_SEPT
SEPT
ANT
INF
LAT
POST
-2
-7
-4
-6
-10
-6
-5
-7
-9
-1
GLPS_LAX -5.0 %
GLPS_A4C -4.7 %
GLPS_A2C -4.6 %
GLPS_Avg -4.8 %
AVC_MEAS = 299 msec
FR_min = 57
HR_aplax = 76
PSD = 63 msec
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Fig. 3.5 Strain imaging using 2D speckle-tracking echo—in this patient with amyloidosis, the global mean longitudinal peak strain is severely reduced at −4.8%

shortening (%FS) can be calculated—values for FS are typically half the value of the LVEF in the non-remodeled heart, such as the donor heart after orthotopic transplantation. Fractional shortening measured from M-mode echo is much less relevant in patients with regional contractile abnormalities, as the degree of shortening in one plane may be completely different from that in another. Nowadays, most echo laboratories routinely measure LVEF by either the biplane 2D method (Simpson's biplane method of discs) or by 3D volumetric measurements, which have been shown to be highly-reproducible. LVEF is highly-dependent on loading conditions and reflects myocardial contractility *only* under the loading conditions at the time at which it is measured. Hence, interpretation of LVEF must be done in the context of those conditions, which may include consideration of the actions of sedative or anesthetic drugs, inotropic agents and valve lesions. For example, in the volume-overloaded heart, such as in severe mitral or aortic regurgitation, LVEF may be elevated, in accordance with the Frank-Starling Law.

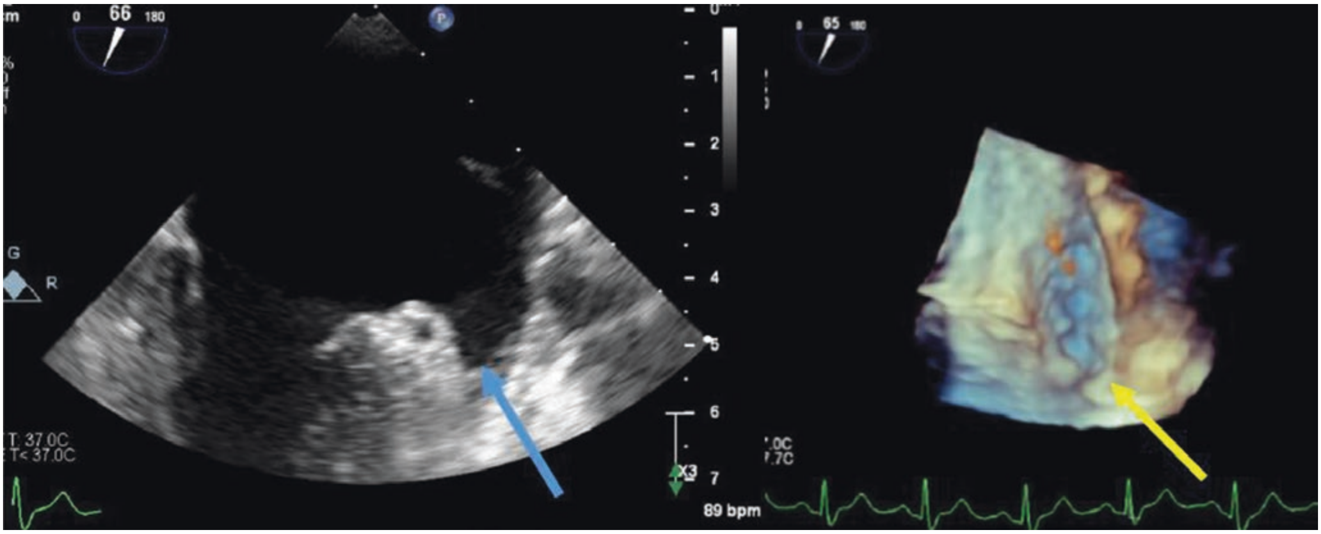


Fig. 3.6 2D transesophageal echocardiography (TEE) of the left atrial appendage showing echoes suspicious for thrombus (yellow arrow) and corresponding 3D TEE confirming that the suspicious "mass" is in fact part of the wall of the appendage (blue arrow)

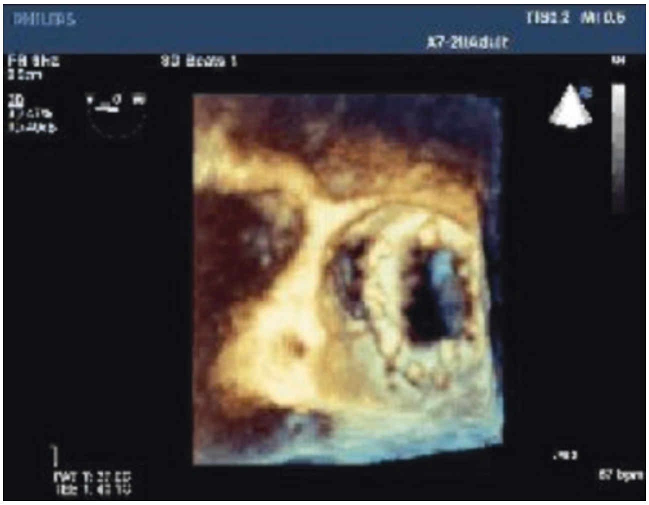


Fig. 3.7 Dehiscent mitral prosthesis seen by 3D transesophageal echocardiography

With the advent of new techniques it has become clear that there are parameters which show abnormalities earlier in the course of LV systolic dysfunction, before there is a change in LVEF or the development of obvious regional abnormalities. Early systolic dysfunction can be detected by assessing abnormalities of long axis function or by assessment of strain using 2D speckle tracking echo. The latter has been shown to be particularly useful in identifying early dysfunction in patients receiving cardiotoxic drugs to treat cancers, and perhaps more relevant to the surgeon, it is becoming clear that even in the presence of an apparently-normal LVEF, subtle abnormalities of strain are predictive of poorer functional outcomes after mitral surgery. It is likely that pre-operative strain measurements will be recognized as valuable prognostic indicators.

Indices of Global Contractility

The rate of development of LV pressure (LV dP/dt) during systole can be assessed from the slope of the mitral regurgitant Doppler waveform (Fig. 3.8). Normal values are >1200 mmHg/s, mild impairment 800–1200 mmHg/s, moderate impairment 600–800 mmHg/s and severe impairment <500 mmHg/s.

The Myocardial Performance Index or *Tei index* is the ratio of the sum of the isovolumic contraction time (ICVT) and the isovolumic relaxation time (IVRT) to the ejection time.

$$\text{Myocardial Performance } (\text{Tei}) \text{ Index} = \text{IVCT} + \text{IVRT} / \text{Ejection fraction}$$

The IVCT is prolonged in systolic dysfunction and the IVRT is prolonged in both systolic and diastolic dysfunction i.e. when there is ventricular dysfunction, the heart spends relatively less time ejecting blood. Tei index is less load-dependent than some parameters, but more time-consuming to calculate and so not performed routinely in most departmental "minimum standards" studies.

Systolic Strain

Global longitudinal strain has now been shown to be a more subtle method of identifying early systolic dysfunction than LVEF. It can also be used prognostically; in a study of heart failure patients every 1% increase in mean GLS was shown to be associated with a 5% decrease in mortality. However, one problem with strain analysis by echocardiography is that currently available proprietary software packages do not give the same results. Hence a patient who is undergoing serial scans for monitoring of function should always have strain analysis done using the same software package.

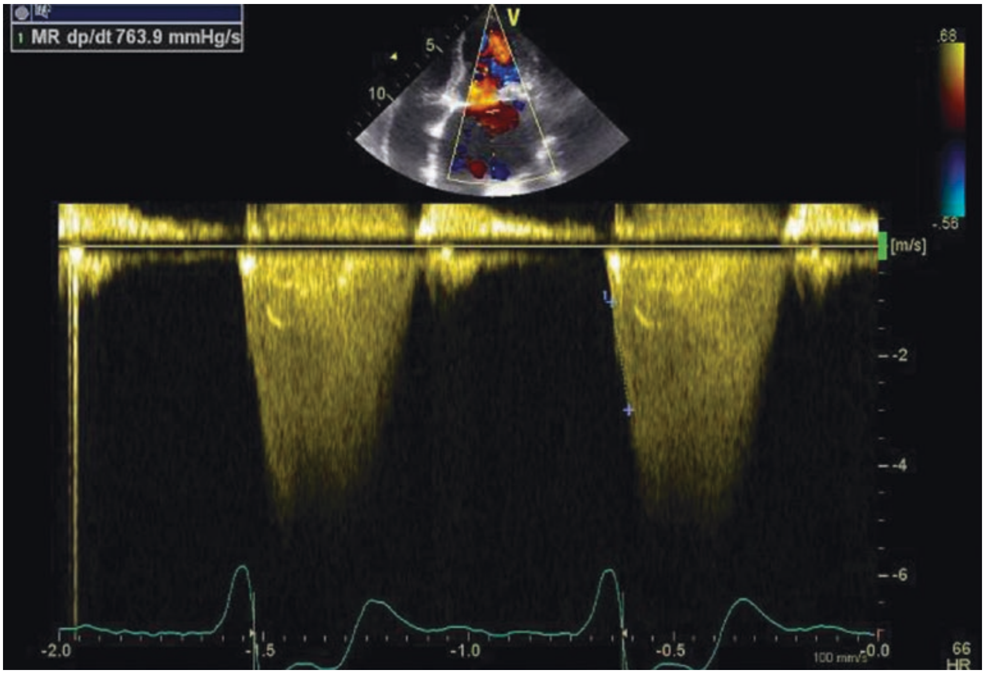


Fig. 3.8 Measuring the LV dP/dt from the mitral regurgitant signal

Regional Contractile Function

Regional/segmental contractile abnormalities are most commonly seen in ischemic heart disease and represent areas of full or partial thickness myocardial infarction. There are some other more unusual causes of regional abnormalities of contraction but these are less frequently encountered in a surgical setting. The assessment of regional abnormalities has traditionally relied on the experienced eye of the echocardiographer but assessment of endocardial motion alone can be misleading as, in cases where there is a limited segmental infarction, the areas of myocardium adjacent to the infarcted segment may appear to move well but in reality this is due to these regions being tethered to adjacent uninfarcted regions which drag them in. In recent years, software advances have allowed the measurement of segmental systolic strain and strain rate. Demonstration of segmental strain abnormalities gives added confidence to the sonographer when diagnosing a regional abnormality of contraction.

Right Ventricular Systolic Function

The right ventricle (RV) is structurally more complex than the left ventricle (LV) and consequently is more difficult to assess by noninvasive imaging. However, RV function is of great importance, because in any condition affecting the left heart, the addition of impaired RV function increases mortality. As with the LV, all parameters we can currently measure are load dependent. Fractional area change (FAC, normal >31%) and tricuspid annular plane systolic excursion (TAPSE, normal >15 mm) are two easily measured parameters, although studies have shown significant variation in the values which predict outcomes in a variety of clinical contexts. As a result, despite the availability of advanced software packages, 3-dimensional volumetric analysis and strain imaging, many surgeons remain most comfortable with the subjective and qualitative opinion of a trusted and experienced echocardiology colleague.

Diastolic Function

The importance of diastolic function in the surgical patient has been increasingly recognized in recent years. It is assessed echocardiographically by measuring the transmitral Doppler E and A waves, and the tissue E' velocity, usually from the lateral mitral annulus. A lateral E/E' value of <10 is normal, values of >15 are abnormal and values of 10–15 represent a "grey area" where there is an increased likelihood of raised filling pressures. The time taken for peak early filling velocity to fall back to zero, the *early deceleration time* is another important parameter. When prolonged, it indicates impaired relaxation and when shortened it may indicate restrictive filling, if the E/A ratio is >2.0 and intraventricular relaxation time is abnormal. If a restrictive filling pattern, also known as a "pseudonormal" pattern, is suspected, a Valsalva manoeuvre should be performed and this should reduce the early filling velocity such that the E/A ratio becomes <1.0. Most patients with abnormal systolic function have some concomitant filling abnormality, and some increase in ventricular stiffness with impairment of relaxation (mild or Grade I diastolic dysfunction) is "normal" with ageing, but diastolic abnormalities may predominate in patients with LVH such as HCM, aortic stenosis and infiltrative disorders e.g. amyloidosis. In such patients, the impaired ventricular relaxation means that they are highly-dependent on atrial contraction for LV filling, and if they develop atrial fibrillation perioperatively, this can be very difficult to manage, resulting in a downward spiral where increased intravenous filling and inotropes fail to produce an increase in cardiac output. In addition, the surgeon may encounter myocardial protection issues in patients with significant LVH and this may exacerbate the diastolic dysfunction of an already-impaired ventricle. Detailed descriptions of diastolic filling patterns indicative of different degrees of dysfunction can be found in any standard echo textbook. However, from the surgeon's point of view, it is more useful simply to know if diastolic function is normal, mild, moderately or severely impaired as this is likely to have an impact on the patient's postoperative/intensive therapy unit (ITU) course.

Assessment of Valve Pathology

Aortic Stenosis

The appearance of the valve is considered first—the morphology and motion of the leaflets, any degenerative changes and the degree of calcification, which is categorized qualitatively as mild, moderate or severe. Color flow Doppler is used to assess turbulence through the valve and then pulse and continuous wave Doppler is used to measure the velocity of blood flow in the left ventricular outflow tract (LVOT) and through the valve respectively. The pressure drop or "gradient" across a narrowed valve is calculated using a simplified Bernoulli equation, where pressure drop (gradient) $\mathbf{\Delta P = 4V^2}$ (V is the maximum velocity of blood flow through the valve) (Table 3.2). In cases where the LVEF and flow rate are normal, a velocity of 4 m/s across the aortic valve (gradient of 64 mmHg) is indicative of severe aortic stenosis (AS). The shape of the CW Doppler waveform is also a clue to severity—as AS advances from "just-about-severe" to "critical" the shape of the trace changes from being asymmetrical with a faster upstroke to becoming symmetrical or "dagger-shaped" (Fig. 3.9) However, in many cases, the LVEF and flow rate are reduced and in these cases it can be much more difficult to appreciate the degree of valve stenosis. Other useful measures are the effective orifice area (EOA) and the dimensionless velocity index (Table 3.3). Calculation of EOA is done using the continuity equation, shown below, where CSA is the cross-sectional area of the LVOT, VTI_1 is the subaortic velocity-time integral and VTI_2 is the transaortic velocity-time integral.

$$\text{Flow-corrected EOA} = \text{Subaortic CSA} \times VTI_1 / VTI_2$$

The calculation uses the square of the radius of the LVOT, which relies on accurate measurement of the LVOT diameter. Any error in this measurement is compounded by the squaring operation and hence is a significant source of error in the calculation of EOA. The dimensionless velocity index is the ratio of maximum flow velocity in the LVOT to maximum flow velocity through the stenotic valve. It eliminates error due to inaccurate measurement of the LVOT diameter.

Table 3.2 Examples of surgically-relevant information obtained by echocardiography in different patient groups[a]

Patient group	Information obtained by echocardiography	Relevance to surgeon
Ischemic heart disease for revascularization	Global and regional left ventricular function, LVEF	Impaired ventricular function is a significant risk factor for decreased survival; surgeon may choose not to revascularize fully-infarcted areas (especially if this would be technically-difficult or there is the need to reduce bypass time)
Mitral regurgitation	Left and right ventricular function; severity and mechanism of regurgitation, tricuspid valve function	Reduced left and right ventricular function may result in difficult wean from bypass; RV failure may prolong intensive care; tricuspid annuloplasty may be performed if tricuspid annulus is dilated >40 mm
Aortic stenosis	Aortic valve and root dimensions, myocardial thickness, diastolic function	Choice between prostheses; valve or root replacement; moderate-severe left ventricular hypertrophy may cause myocardial protection issues; diastolic dysfunction may prolong ITU stay if filling is very impaired especially if there is perioperative atrial dysrhythmia
Aortic regurgitation	Aortic root dimensions, valve morphology, ventricular function	Choice of operative strategy—valve replacement or repair, root replacement, valve-sparing root surgery?
Endocarditis	Evidence of complications e.g. fistulae and abscess formation	Informs operative planning regarding likely length and complexity of surgery

ITU intensive therapy unit, *LVEF* left ventricular ejection fraction, *RV* right ventricular

[a] This is NOT comprehensive

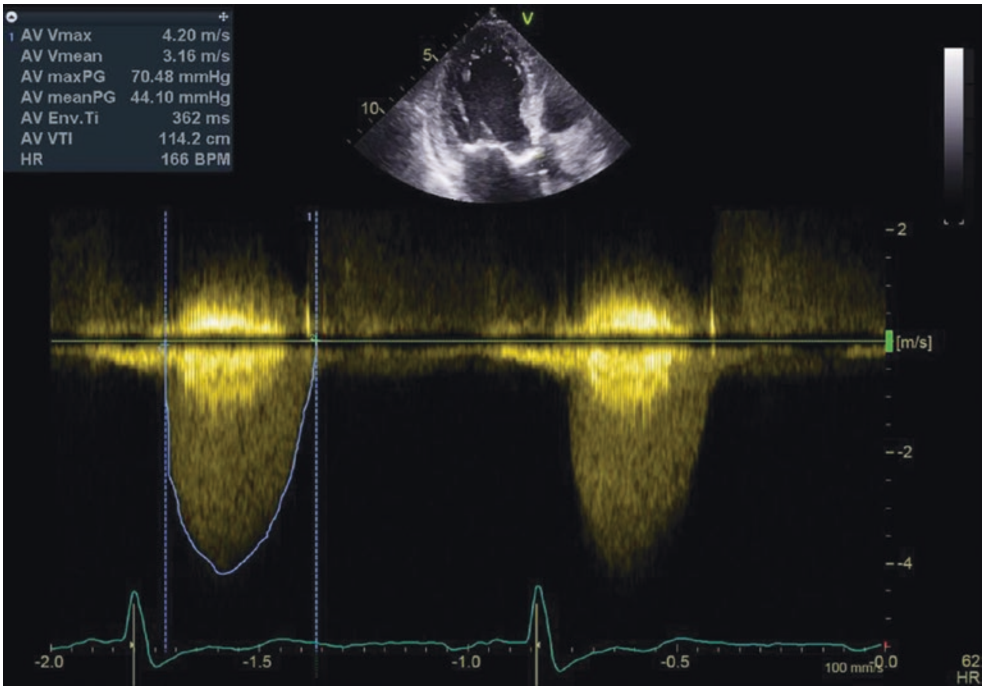


Fig. 3.9 The symmetrical "dagger-shaped" CW Doppler trace seen in very severe aortic stenosis

Table 3.3 Criteria for assessing severity of aortic stenosis

Criterion	Mild	Moderate	Severe
Vmax (m/s)	2.5–3.0	3.0–4.0	>4.0
Peak gradient (mmHg)	<40	40–64	>64
Mean gradient (mmHg)	<25	25–40	>40
Effective orifice area (cm^2)	>1.2	0.8–1.2	<0.8
Dimensionless velocity index	>0.5	0.25–0.5	<0.25

The 2017 ESC Guidelines on the management of valve disease [3] recognizes four different categories of aortic stenosis, based on flow and LVEF (Table 3.4).

Aortic Regurgitation

The etiology of aortic regurgitation generally falls into one of two broad categories: valve abnormalities (congenital, infective, rheumatic, degenerative and other rarer causes) and root dilatation. The latter is commonly associated with longstanding hypertension, as well as being a feature of Marfan's, Loeys-Dietz and Ehlers-Danlos syndromes along with other collagen vascular disorders not yet genetically-characterized. Aortic valve and root morphology is visually assessed and aortic dimensions are measured at standard levels: the LVOT, the "annulus", across the sinuses of Valsalva, the sino-tubular junction and the ascending aorta (Fig. 3.10). The vena contracta of the color jet is measured and the width of the regurgitant jet is also expressed as a percentage of the LVOT diameter 5–10 mm below the valve (Fig. 3.11). As with mitral regurgitation, the PISA method may be used to calculate EROA and regurgitant volume. The most commonly-quoted parameter is the pressure half-time, measured from the CW Doppler trace. This can be misleading in advanced disease, because the pressure half-time is shortened in the presence of raised end-diastolic pressure. The density of the regurgitant signal is also compared visually to the density of the forward flow trace. LV volumes and LVEF are also important because a hyperdynamic ventricle suggests severe regurgitation and a dilated ventricle usually means the regurgitation is chronic. Perhaps the most sensitive parameter is the demonstration of pandiastolic flow reversal in the descending limb of the aortic arch by color flow or PW Doppler. Parameters used to assess the degree of aortic regurgitation are shown in Table 3.5.

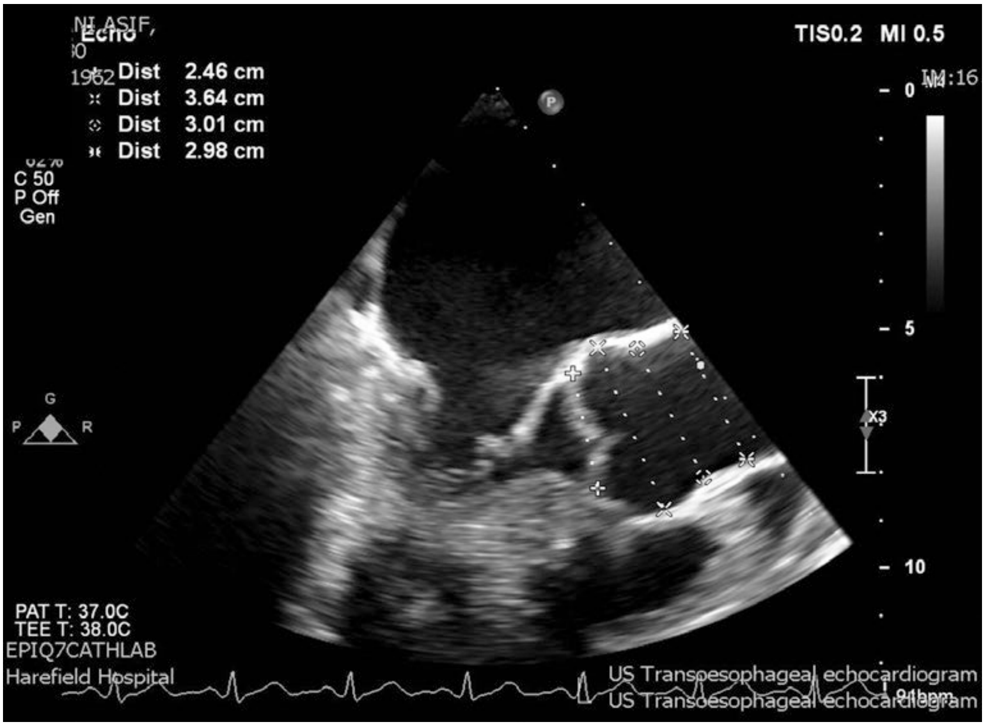
Mitral Stenosis

This is seen less frequently in the West due to the decline in prevalence of rheumatic heart disease. However, worldwide it continues to be the commonest cause of mitral stenosis (MS). The "hockey stick" appearance of the anterior mitral leaflet is diagnostic (Fig. 3.12). Echocardiography is excellent for demonstrating calcium in the leaflets and subvalvar apparatus and the degree of stenosis may be assessed using Doppler parameters such as pressure half-time (mitral valve area (cm^2) = 220/pressure half-time (ms)) and planimetry. (Severe MS <1 cm^2, moderate 1.0–1.5 cm^2, mild >1.5 cm^2) When considering whether balloon valvuloplasty may be

Table 3.4 Types of aortic stenosis recognized in the 2017 ESC Guidelines for the management of valve disease

Type of aortic stenosis	Mean gradient	Area	Flow	LVEF	Notes
High PG	>40 mmHg	<1 cm^2	Normal/reduced	Any	For surgical intervention, bearing in mind that lower LVEF increases risk
Low-flow, low PG, low LVEF	<40 mmHg	<1cm^2	Reduced (SVi < 35 ml/m^2)	<50%	Role for DSE
Low flow, low PG, Normal LVEF	<40 mmHg	<1cm^2	Reduced	≥50%	Older, female, LVH, BP MSCT calcium score
Normal flow, low gradient, normal LVEF	<40 mmHg	<1cm^2	Normal (SVi >35 ml/m^2)	≥50%	Moderate AS (in general..)

AS aortic stenosis, *BP* blood pressure, *DSE* dobutamine stress echo, *LVEF* left ventricular ejection fraction, *LVH* left ventricular hypertrophy, *MSCT* multislice computed tomography, *PG* peak gradient, *SVi* stroke volume index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Harefield Hospital
US Transoesophageal echocardiogram

Fig. 3.10 The normal aortic root seen in a TEE lower esophageal view at approximately 120° showing aortic measurements made at various standard levels

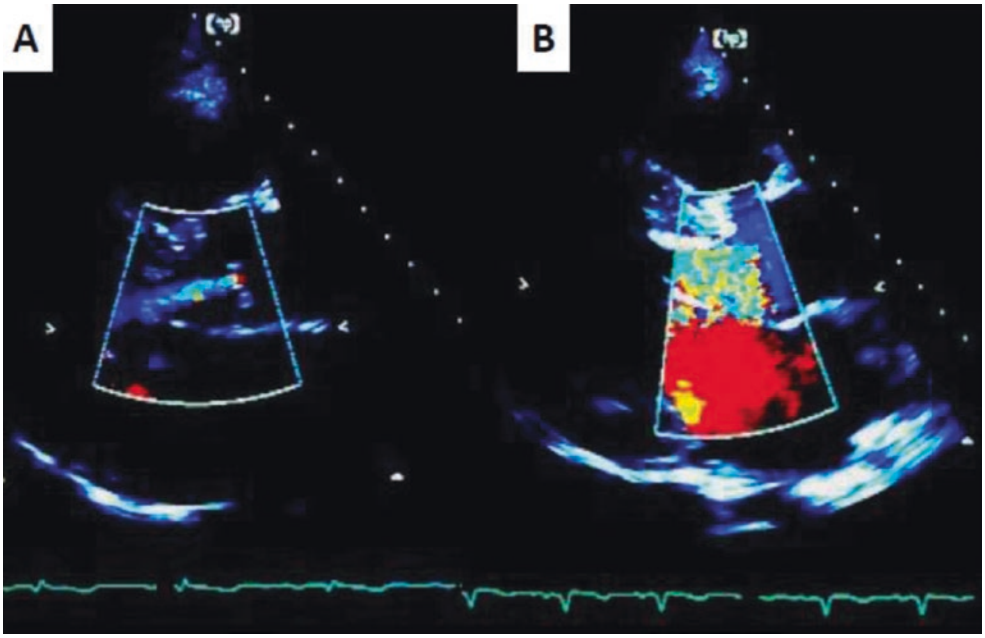

Fig. 3.11 Jet width in the left ventricular outflow tract in aortic regurgitation. Panel **a**—mild, Panel **b**—severe

Table 3.5 Criteria for assessing severity of aortic regurgitation

Criterion	Mild	Moderate	Severe
Jet width as % of LVOT width	<30	31–60	>60
Pressure half-time (ms)	>650	250–650 BUT this is a very grey area, with mild and severe AR sometimes falling into this category by PHT measurement, which can be affected by a number of other factors such as LVEDP	<250
Density of CW Doppler trace	Faint or incomplete	Complete but not as dense as forward flow	As dense as forward flow Doppler trace
Vena contracta (mm)	<3	3–6	>6
Flow reversal in the descending limb of the arch	None/early “flash” due to aortic recoil	Present but not pandiastolic	Pandiastolic/long diastolic tail

AR aortic regurgitation, *LVEDP* left ventricular end-diastolic pressure, *LVOT* left ventricular outflow tract, *PHT* pulmonary hypertension

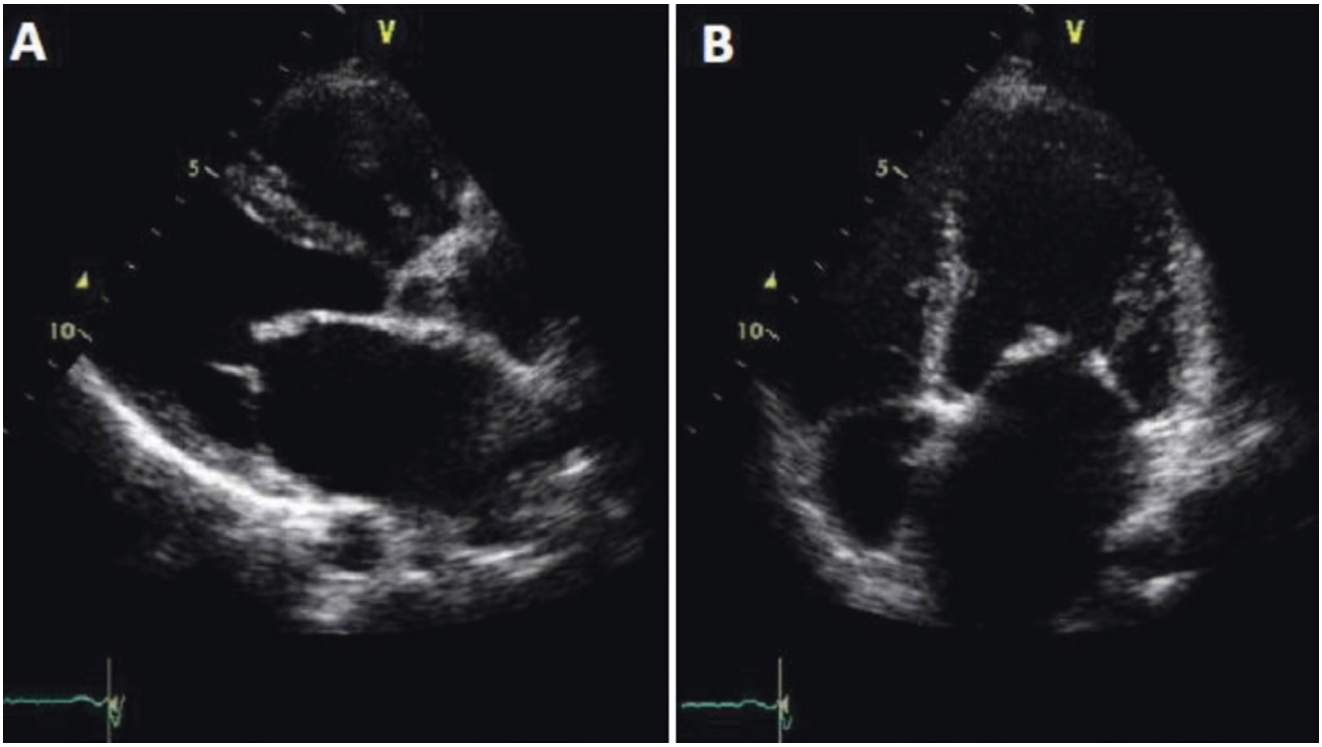

Fig. 3.12 Parasternal long axis (**a**) and 4-chamber (**b**) views showing a rheumatic mitral valve—note the typical “hockey stick” appearance of the anterior leaflet

more appropriate for the patient than surgery, the Wilkins Score may be used to assess the likelihood of a favorable outcome. The score is based on echo appearances and rates the valve for leaflet mobility, leaflet thickening, calcification and subvalvar involvement. The maximum score for each category is 4 and the minimum is one, hence the scores range from 4 to 16. A score of 8 or below is predictive of a favorable outcome with balloon valvuloplasty. Some measurements may be less reliable in the presence of other valve lesions, and in many cases, a detailed examination by transesophageal echocardiography is helpful to clarify the situation.

Mitral Regurgitation

Echocardiography is key to distinguishing between primary degenerative mitral valve disease and secondary mitral regurgitation (MR) due to abnormalities of LV geometry and function (Fig. 3.13). A systematic approach to the assessment and grading of MR involves assessment of the morphology of the valve, the annulus, leaflets, subvalvar apparatus and papillary muscles. Color flow Doppler is used to demonstrate the regurgitant jet, although relying on this alone for the estimation of severity of MR is inadvisable. The most distinguishing parameter for severity of MR in the awake patient is the

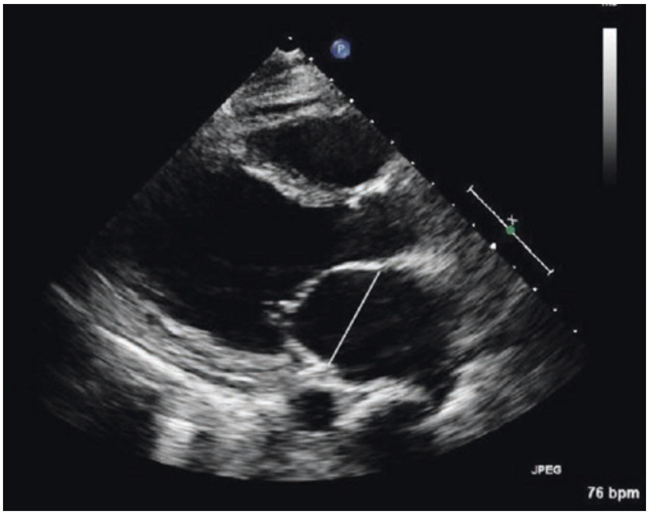

Fig. 3.13 Mitral leaflets tethered in to the left ventricle due to adverse ventricular geometry and increased interpapillary muscle distance. The annular pane is marked by the white line

transmitral PW Doppler trace. In severe MR, the early filling (E wave) should be ≥1 m/s. An assessment of pulmonary pressure should be made from the tricuspid regurgitant signal, if present. The PISA equation can be used to calculate effective regurgitant orifice area and regurgitant volume. It must be remembered that for the same calculated MR regurgitant volume, the prognosis for degenerative MR is better than that for ischemic functional MR. This has led many experts to suggest that "moderate MR" in ischemic patients is "in reality severe MR". However, the author is of the opinion that the MR volume is exactly what it is measured as—it is the prognosis that differs depending on the etiology. The box below is a list of suggested questions that the surgeon should ask him/herself when reviewing echo images during heart team discussions of mitral regurgitation cases.

- What is the jet width?
- How dense is the Doppler trace?
- What are the EROA and regurgitant volume by PISA calculation?
- How big is the left atrium?
- Is the filling pattern consistent with severe MR?
  - Short filling time?
  - High-velocity E wave?
- Is there presystolic MR?
- Is there systolic blunting/reversal of the pulmonary venous flow signal?
- What is the mechanism?

Transthoracic echocardiography is more than adequate to assess the severity of native mitral valve regurgitation, but in patients who are likely to require surgical or percutaneous mitral intervention, the exact mechanisms of the MR are best shown by a detailed transesophageal echo, including 3D imaging or reconstruction.

Tricuspid Valve Assessment

As with other valves, the first question is whether the valve is morphologically normal. Abnormalities of the leaflets should be noted, along with assessment of the annulus and RV. Causes of tricuspid regurgitation (TR), as with MR fall in to two broad categories—primary valve disease and secondary ventricular/functional etiology. Echo criteria for grading the severity of TR include the density and shape of the CW Doppler trace, the vena contracta width and the presence of hepatic vein systolic flow reversal or blunting. Pulmonary artery systolic pressure (PASP) may be estimated by measuring the pressure drop across the tricuspid valve from the TR CW Doppler signal and adding this to the right atrial (RA) pressure estimated from the inferior vena cava (IVC) dimension and inspiratory reactivity. However, in cases of severe chronic TR where the pressures in the RA and RV have virtually equalized, the TR signal is no longer a reliable method of estimating PASP.

Pulmonary Valve Assessment

The normal pulmonary valve is mildly regurgitant. The regurgitant signal may be used to estimate pulmonary artery end-diastolic pressure, using the end-diastolic velocity of the regurgitant signal, whether normal (physiological) or pathological. Pulmonary valvar abnormalities are seen predominantly in patients with congenital heart disease, although there are a few conditions which are known to affect predominantly right-sided valves, including carcinoid syndrome and device-associated infective endocarditis.

Infective Endocarditis

Echocardiography has long been the first-line imaging test performed on patients with suspected endocarditis. Despite this, it was only relatively recently that the criteria for diagnosing endocarditis were modified to include echo evidence of infection as one of the major criteria. Any of the four native valves in the heart can be infected, but the initial source of infection is elsewhere in the body—the heart is very rarely the primary source [2]. In the mid to late twentieth century, the commonest suspected source of bacteremia was the mouth, with oral streptococci being the usual culprits. In some cases, a temporal relationship to dental work can be demonstrated. Skin organisms such as staphylococci and in particular the very invasive S. aureus were the other commonly-seen infective organisms—often in association

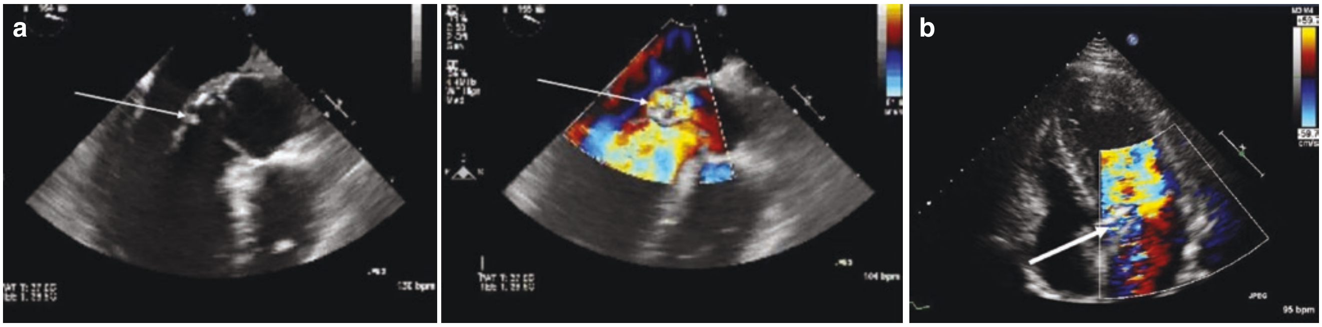

Fig. 3.14 (**a**) Aortic root abscess (arrow) seen by TEE with color flow Doppler and severe aortic regurgitation in a patient with infective endocarditis. (**b**) In this patient with aortic endocarditis, a fistula (arrow) has formed between the aortic root and the left ventricle

with intravenous drug use, and primarily affecting the venous or right side of the heart. However, many other organisms, both bacterial and fungal, are known to be causally implicated in endocarditis. Recently, there has been a significant rise in infections in patients who have implantable cardiac devices. This so-called "device-associated endocarditis" is commonly caused by skin organisms. Prosthetic material in the heart, whether it be artificial valves, Dacron patches and conduits or pacing leads may all present focuses for infection. Organisms in the bloodstream become attached to the prosthetic material and form infected clumps composed of organisms, fibrin, and blood cells, termed a *vegetation*. Once prosthetic material is involved, it is virtually impossible to clear the infection and effect a cure without removing the infected material. Despite advances in virtually all fields of medicine and in particular in the field of infectious diseases, the mortality from infective endocarditis has remained depressingly constant at 25–40%, with infected prosthetic material, such as heart valves, carrying the highest mortality and morbidity rates. The reasons for this include delay in diagnosis and the increased age and hence frailty of many patients, especially in the device-associated infection group.

Echo Findings in Endocarditis

Typically, echocardiography demonstrates vegetations as mobile intracardiac masses, often associated with any prosthetic material or artificial valve. The size, shape and mobility of vegetations varies greatly depending on a number of factors including the type of organism involved, the exact site of the lesion and the amount of free space in which the vegetation can move. Other findings reflect the damage caused to endocardial structures by the invasive infecting organism—these findings include fistulae between chambers, abscesses of the aortic root and mitral annulus/leaflets, destruction of tissue e.g., valve leaflets, and dehiscence of prosthetic valves or graft material. The consequences of such destruction often produces new regurgitant valve lesions, paravalvar leaks, abscesses and shunting between chambers and/or great vessels—demonstrable by abnormal color flow Doppler findings (Fig. 3.14a, b).

Transesophageal echocardiography (TEE) is significantly more sensitive than transthoracic echo for visualizing vegetations (approximately 90% vs. 60% respectively), especially in the presence of prosthetic material which causes echo artefacts. Real time 3D TEE has proven to be very useful in this regard, and is also useful for confirming paravalvar leaks.

It must be noted that, despite advances in echo, it is entirely possible for echocardiographic appearances to be normal in the presence of intracardiac infection, hence, the diagnosis of infective endocarditis rightly remains a clinical one.

Pericardial Disease

Echocardiography is the technique of choice to confirm the presence of pericardial effusion. In the cardiac surgical patient this is most commonly a request made during the early post-operative course, but there are some later-presenting cases at 3–6 weeks post-operatively due to Dressler's syndrome. Preoperative assessment of effusion is also made in the oncology patient, or patients with other pericardial diseases. Echo plays two roles: firstly, confirming the presence of pericardial fluid and differentiating it from pleural fluid, and secondly assessing any haemodynamic effects of the effusion. The accumulation of pericardial fluid can cause tamponade, a clinical syndrome in which elevated intrapericardial pressure restricts filling of the heart, hence reducing cardiac output. It cannot be sufficiently emphasized that tamponade is a clinical diagnosis, based on the findings of Beck's triad: true or relative hypotension, distended neck veins and muffled or absent heart sounds, often with an associated tachycardia. Unfortunately for those relying on clinical examination in the postoperative patient, heart sounds may be less distinct due to inflammation and tissue edema, bruising or iv catheters may make it difficult to appreciate the neck veins, the patient may be paced and there are other reasons for hypotension. Nevertheless, tamponade is relatively unlikely in a completely well, asymptomatic postoperative patient with stable blood pressure and heart rate.

The typical findings are of an echo-free space around the heart (Fig. 3.15). The first priority is to distinguish pericardial from pleural fluid. If the echo-free space extends behind the aorta, then this is a pleural collection. The size of the space is directly correlated with the fluid volume. In cases where this is large, the ventricle may appear to be moving within the fluid—the so-called "swinging heart". In the postoperative patient the fluid may be circumferential or loculated, and associated with the right or left sides of the heart or both. The sonographer will assess the volume of fluid, and then any hemodynamic effects by assessing cardiac inflow and outflow Doppler across the mitral, tricuspid and aortic valves during respiration. Typically, there should be <20% variation in the amplitude of the inflow Doppler during respiration. However, in the post-operative patient, this may be confounded by the patient's filling status and by positive pressure ventilation, which splints the IVC. The most significant finding in the awake, spontaneously-breathing patient is of an engorged IVC which does not reduce in size when the patient performs a short, sharp intake of breath, the "sniff test".

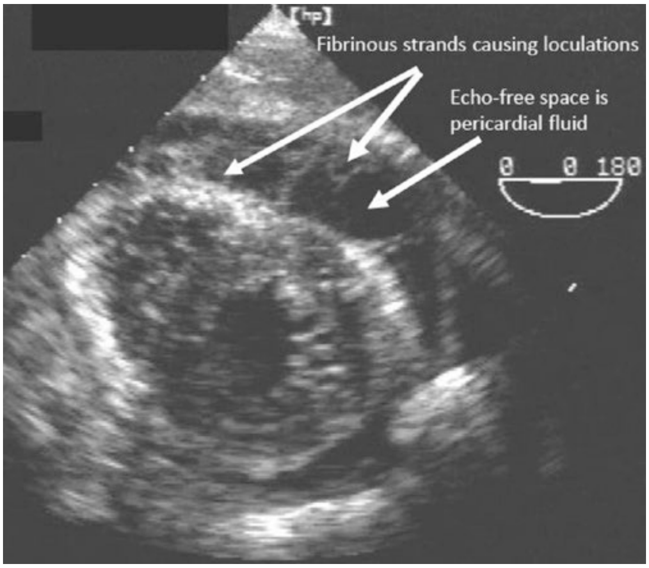
[hp]
Fibrinous strands causing loculations
Echo-free space is pericardial fluid
0 0 180

Fig. 3.15 Loculated pericardial effusion seen by TEE in transgastric view

Pericardial constriction can be challenging to diagnose by echocardiography, but as mentioned above, tissue Doppler imaging can distinguish between constriction and restriction in many cases.

Masses

The most commonly encountered masses in the heart are thrombi due to low flow or thrombophilia traits. Thrombi are particularly seen in the left atrial appendage of patients in atrial fibrillation and lining the wall of akinetic aneurysmal infarcted areas of the left ventricle. Contrast may be used to confirm the presence of thrombus. Tumors of the heart are much rarer but may be either primary, such as myxomata and fibroelastomata (Fig. 3.16), or secondary such as renal or breast metastasis and malignant melanoma.

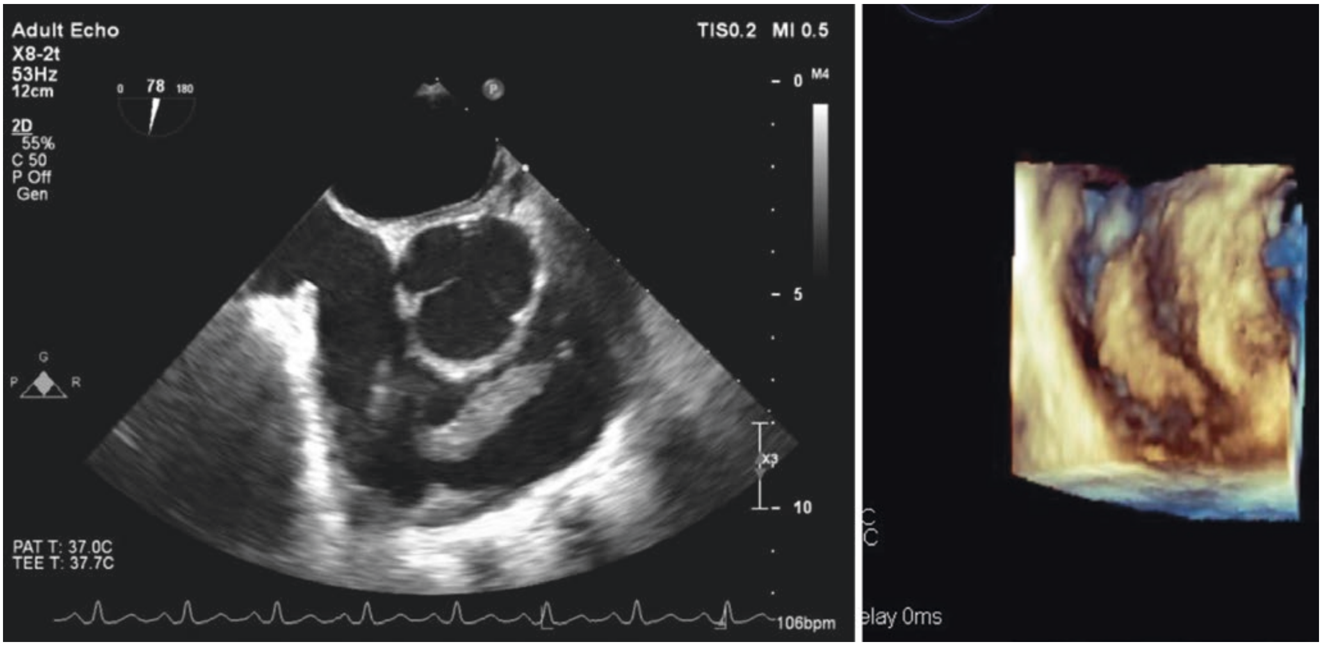

Fig. 3.16 2D and 3D echo of a mass in the right ventricle in a patient who presented with pulmonary embolism—this was a myxoma

Contrast Echocardiography

In echocardiography, contrast is used for the following reasons:

- *Ventricular opacification:* To delineate the endocardial border in patients with suboptimal image quality/poor acoustic windows. This type of contrast is typically a commercially-produced suspension of microbubbles of inert gas such as sulphur hexafluoride which, when administered intravenously, is highly echogenic and causes the blood pool to show up as white on greyscale 2D echo images with appropriate adjustment of power settings. The reproducibility of 2D measurements of LV biplane volumes is increased by using contrast.
- *Myocardial perfusion:* This uses the same type of contrast as described above to identify stress-induced perfusion abnormalities. This is a highly-specialized technique, even within the world of echocardiography, and requires considerable experience to interpret. Even then, the technique lacks specificity, although the sensitivity is higher than some other noninvasive techniques.
- *Identification of PFO:* Most echocardiologists prefer to use a “bubble” contrast agent, typically composed of 8 ml saline mixed with 1 ml air and 1 ml of the patient’s blood, agitated vigorously by mixing through a three-way tap to produce microcavitations which are then injected as a bolus, preferably on release of a Valsalva manoeuvre, which results in rapid, fast venous return to the heart and produces a small R:L shunt in patients with a patent foramen ovale.

Stress Echocardiography

Stress echo is used for two main indications: to look for areas of inducible myocardial ischemia in patients with known or suspected coronary artery disease and to assess the severity and impact of both aortic and mitral valve disease [4]. Both exercise and pharmacological stress are used depending on the clinical indication. In general, if a patient is able to exercise, then this method of stress best mimics true physiology and is to be recommended if the echo laboratory has appropriate equipment. Imaging during stress is technically-demanding and a semi-supine tilting bicycle ergometer is preferable to a treadmill.

Stress Echo for Coronary Artery Disease

The aim of the stress test is to look for evidence of inducible ischemia, which shows itself either as a regional wall motion abnormality affecting one or more coronary territories or, in cases of triple vessel disease and/or if global subendocardial ischemia is induced then the ventricle may dilate and become globally impaired or dyssynchronous. As the intention is to provoke ischemia, the level of either exercise or pharmacological stress is usually increased incrementally until the heart rate reaches at least 85% of age-predicted maximum—if this level is not reached then the sensitivity of the test results are likely to be reduced. An ECG rhythm strip is monitored throughout and many laboratories use continuous 12-lead ECG monitoring. Blood pressure is also measured periodically and a fall, or failure to maintain an increased double-product is an adverse sign.

Various protocols exist and the surgeon is well-advised to get to know the expertise and standard operating procedures of his/her own local echo laboratory.

Stress Echo for Aortic Stenosis

As noted above in the description of types of aortic stenosis, stress echo is used for two reasons in the context of aortic stenosis: firstly, to differentiate severe from moderate valve stenosis in patients with reduced flow due to impaired LV function and secondly to look for evidence of contractile reserve in patients with confirmed severe AS who are being considered for intervention. Stress is usually performed with low-dose dobutamine—often no more than 10 mcg/kg/min is required to give an answer, or very occasionally 15 mcg/kg/min. When looking to confirm a diagnosis of severe AS, the aim is to demonstrate an increase in flow without a significant corresponding increase in effective orifice area, i.e. the EOA remains below 1.2 cm^2 despite an appropriate increase in flow.

Stress Echo for Mitral Regurgitation

Bicycle stress echo is increasingly used in patients with asymptomatic severe degenerative mitral regurgitation to look for evidence of a significant increase in pulmonary pressure with exercise, which would be a clear indication to recommend surgical intervention to repair the valve. In patients with ischemic heart disease and exertional dyspnea, stress echo may show worsening of MR by inducing ischemia [5] (Fig. 3.17).

Other Indications for Stress Echocardiography

Exercise stress echo is a good way to demonstrate exertional LVOT obstruction in patients with hypertrophic cardiomyopathy (HCM) who are being considered for surgical septal myectomy. Stress echo is also beginning to be used to assess RV contractile reserve in patients who are candidates for operations such as mitral valve surgery but who have impaired RV function.

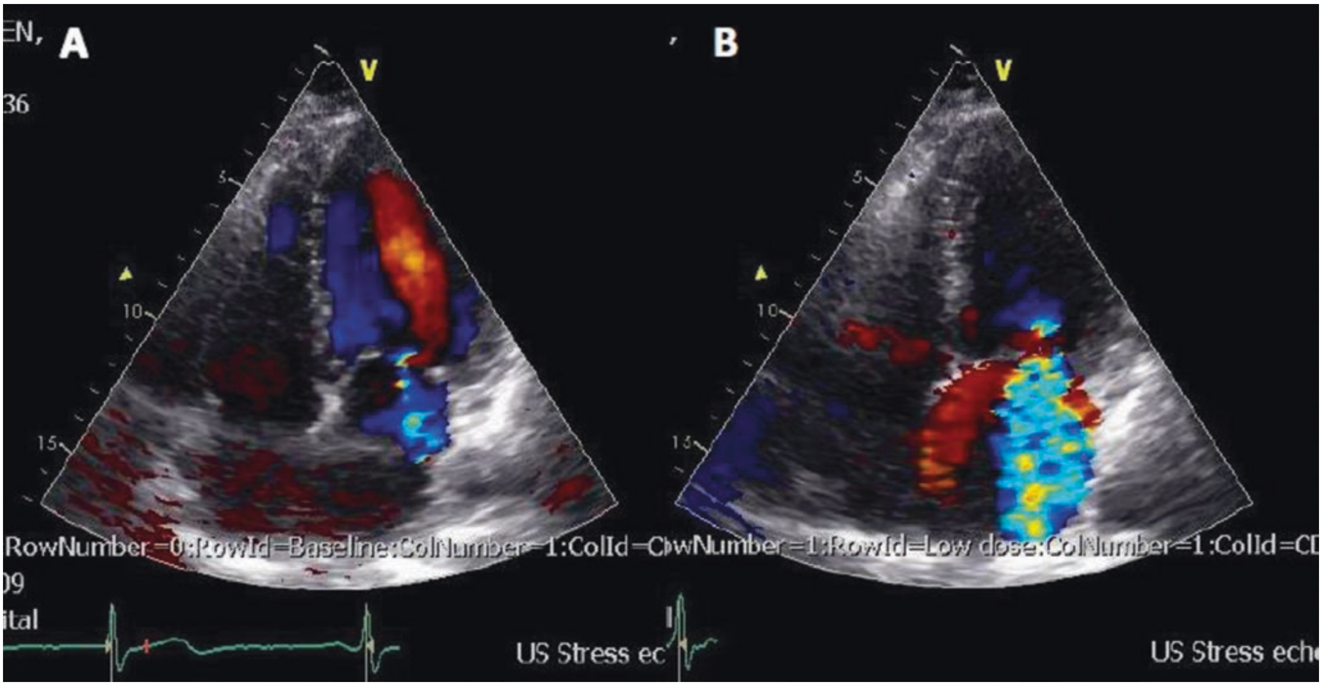
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Fig. 3.17 Rest (**a**) and stress (**b**) color Doppler echo showing worsening of ischemic mitral regurgitation

Transesophageal Echocardiography (TEE)

Pre-operative TEE

Elective pre-operative transesophageal echocardiography is invaluable to the surgeon for planning complex procedures such as mitral valve repair, aortic root repair, and operations for infection [6]. It is preferable in such cases to perform TEE in a planned manner and preferably under awake lightly-sedated conditions so that the physiological effect of valve lesions can be better-appreciated. Developments in software and probe technology mean that real-time 3D imaging provides the multidisciplinary heart team with views of the heart valves, which are very similar to those the surgeon would see when the chest is open (Fig. 3.18). This is particularly helpful in the appreciation of complex mitral pathology, when detailed 3D reconstructions of the valve enable the surgeon to formulate a clear plan in advance of the operation itself (Fig. 3.19). This facilitates discussions with the patient, setting of expectations and better-informed consent.

Intraoperative TEE

This is usually performed and interpreted by experienced cardiothoracic anesthetists. After induction of anesthesia a baseline scan is performed according to standard EACTA/ASE protocol. This scan is not for the purposes of clinical decision-making, except in emergency cases, but is a baseline for later comparison. Many anesthetic and sedative drugs have a mild myocardial depressant effect, and along with the relative hypovolemia caused by fasting prior to surgery, any valve lesions may appear to be significantly less-severe when assessed in the anesthetic room. Right-sided valve lesions such as tricuspid regurgitation are affected even more than left-sided ones, such that even moderate-severe TR may appear to be only mild under anesthesia. For this reason, it is generally inadvisable to change a preoperatively-determined surgical plan based on findings during the on-the-table pre-op TEE.

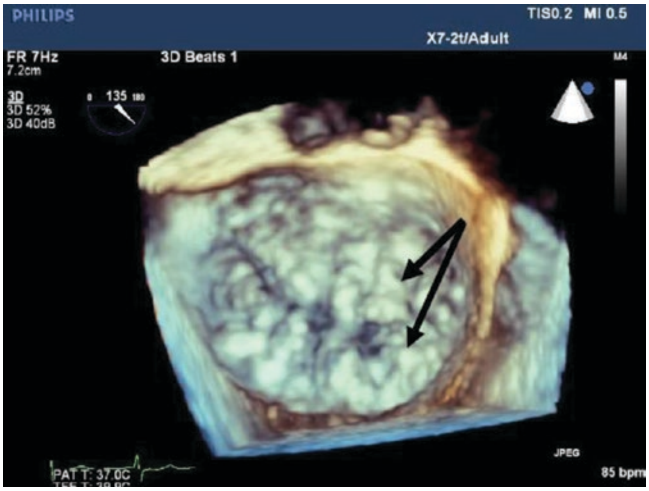

Fig. 3.18 3D TOE of the mitral valve. This en-face "surgeon's view" shows bileaflet prolapse predominantly involving the posterior commissure (arrows)

During surgery, TEE may be useful in identifying the tips of lines or cannulae but in general, once the patient is "on pump", there is no further useful information contributed by

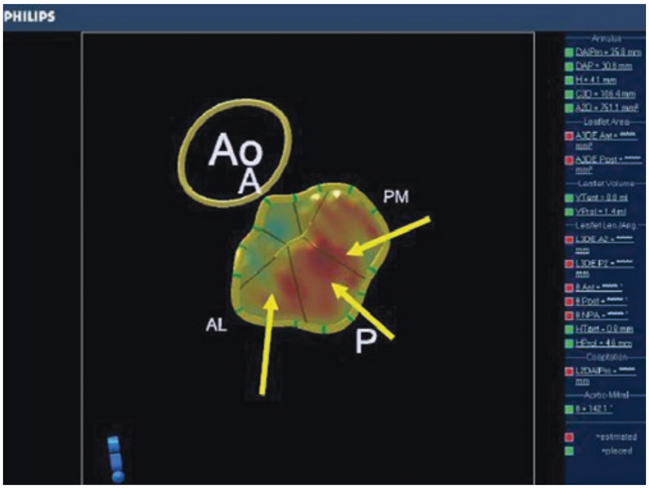

Fig. 3.19 Reconstruction of mitral valve from 3D TEE. The red area (yellow arrows) is prolapsed posterior leaflet

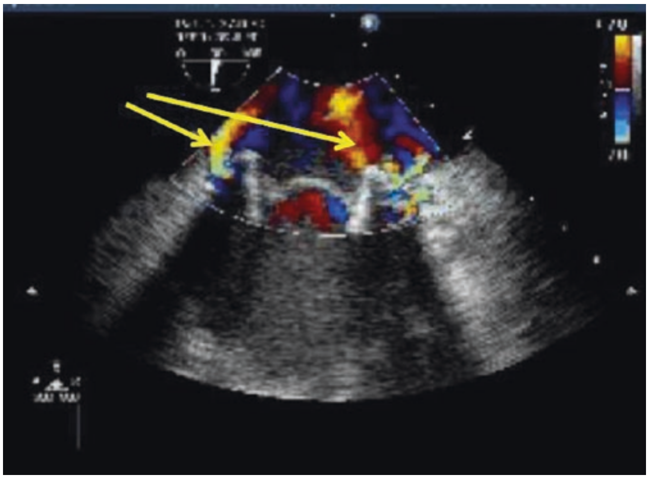

Fig. 3.20 Paravalvar jets (arrows) around a tissue mitral prosthesis

TEE until the end of the procedure and weaning from bypass. At this point there are a number of questions which the surgeon can usefully put to the anesthetist or cardiologist TEE operator:

- What is the left and right ventricular function?
- Is there any new/unexpected wall motion abnormality?
- Can flow in the circumflex artery be demonstrated (especially relevant if a mitral annuloplasty ring has been used)?
- Is de-airing complete?
- Is the valve repair sound?
- Is there any paraprosthetic leak? (Fig. 3.20)

This is not a comprehensive list, as the most relevant and useful information will depend upon the clinical context, exact procedure performed, any technical difficulties and the observations at that time.

Conclusions

Echocardiography, with its emphasis on physiology, is the imaging technique which gives the most information about the *performance* of the heart and its structures. Its safety, patient acceptability and portability—meaning it can be performed wherever required, including in the operating theatre and on the ITU—mean that it is, without question, the most useful of the noninvasive imaging modalities which the surgeon has access to. Its pre-eminence means that it is worthwhile for the cardiac surgeon-in-training to spend some time getting to grips with the fundamentals of the technique, being familiar with the echo appearance of commonly-encountered surgical pathologies, and developing some understanding of the way in which these findings are interpreted. Whilst the cardiac surgeon does not need to be able to perform echocardiograms, he/she must certainly know enough to be able to use the technique to best advantage.

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4

Cardiac Computed Tomography and Magnetic Resonance Imaging

Tarun K. Mittal

High Yield Facts

- Cardiac CT and MRI have emerged as important complimentary imaging techniques to conventional echocardiography and catheter angiogram in imaging the heart and great vessels.
- Both techniques can now be performed with ECG-gating allowing motion free images at acceptable temporal resolution.
- Cardiac CT is best for high spatial resolution delineation of anatomy and has become the non-invasive gold-standard for demonstration and exclusion of coronary artery disease.
- Cardiac CT permits fast acquisition and is particularly suitable for post-operative patient.
- Cardiac MRI provides anatomy, function, and myocardial tissue characterisation.
- Cardiac MRI is the modality of choice for further work-up of patients with heart failure, cardiomyopathies, and certain valvular diseases.
- Both techniques are suitable for pericardial diseases, congenital heart diseases, and cardiac masses.
- CT is best for acute aortic syndromes but for long-term follow-up of aortic aneurysms, MRI may be better due to lack of radiation.
- MRI is free from ionising radiation but may be contraindicated in patients with certain devices.
- The radiation dose with CT is rapidly reducing with newer scanners and benefit may outweigh the risks in certain situations.

Introduction

Both computed tomography (CT) and magnetic resonance imaging (MRI) have found increasing use in imaging of the heart and great vessels besides other parts of the body. Advancement in technology in recent years has continued to make the scans faster with ability to scan the beating heart at a greater spatial resolution. Although both CT and MRI are based on different physics principles with different appearances of various tissues and organs on the images, their application in diseases of the heart and vessels are largely complimentary. Several international guidelines now exist defining their use in clinical practice [1, 2]. This chapter focuses on the salient applications of these techniques essential for a cardiac surgeon in training and practice.

Technology

Computed Tomography (CT)

Just like plain radiographs and angiographic techniques, a CT scanner utilises an X-ray tube at one end which produces the X-rays that pass through the patient and are detected by a row of detectors at the opposite end to produce images [3]. Both the X-ray tube and detector rows are housed in a circular gantry and rotate around the patient table. Most CT scanners in use currently are multi-slice, that acquire multiple images through the body with each rotation, ranging from 4- to 320-slices. The images produced are in axial-plane but as the images are thin (slice thickness of 0.3–0.6 mm), the data is volumetric and can be automatically reconstructed by software (available on PACS or specialist CT software) in coronary, sagittal, oblique, or curved planes, often called multi-planar reformats (MPR) (Fig. 4.1a–d).

A CT scan for the heart and vessels is typically performed with intravenous contrast to opacify the lumen of the cardiac chambers, coronary arteries, and the vessels. The contrast used for CT are iodinated low-osmolar agents and injected in

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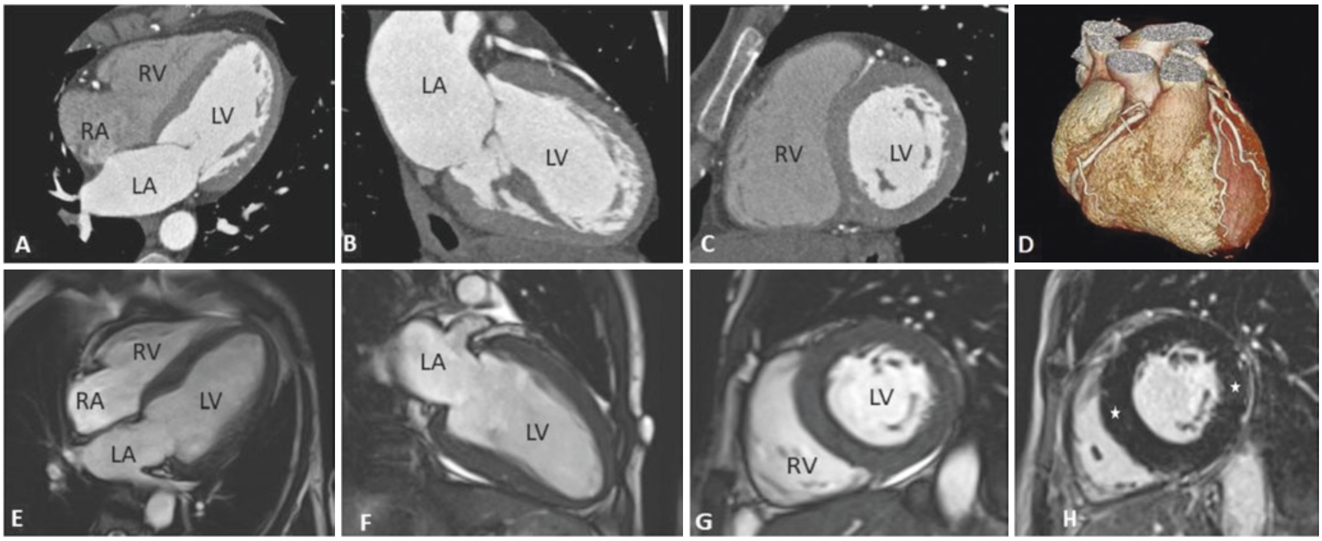


Fig. 4.1 Normal CT cardiac angiogram (**a**–**d**) and MRI (**e**–**h**) images. CTCA Multi-planar reformats in 4-chamber (**a**), 2-chamber (**b**), and short-axis (**c**) views along with 3-D reconstruction (**d**). End-diastolic frames from cardiac MRI cine 4-chamber (**e**), 2-chamber (**f**), short-axis (**g**), and delayed post-contrast images with normal myocardium showing low signal intensity (**h**, Asterix). *CTCA* Computed angiography cardiac angiogram, *RA* right atrium, *RV* right ventricle, *LA* left atrium, *LV* left ventricle

veins, mostly the antecubital fossa. Although minor allergic reaction can occur with contrast, serious anaphylactoid reactions are very rare (<1:40,000). Caution is to be borne in patients with renal impairment, where oral or intravenous hydration is advised. In some situations, such as for assessment of calcification in pericardium, haemorrhage in the wall of aorta (intra-mural haematoma), or just for assessment of the lung parenchyma, a non-contrast CT is helpful.

As the rotation of x-ray tube has become faster (typical speed now is 0.25–0.35 ms), it has become possible to acquire the scans with ECG-gating. This allows motion free images of the heart and aorta, commonly in diastolic phase of cardiac cycle if the heart-rate is reduced to 65 bpm or less with beta-blockers. This has become the basis of CT coronary angiography and obtaining motion free images of the thoracic aorta in patients with suspected Type A dissection. For rest of the indications, CT scans are acquired without ECG-gating.

As CT is a technique involving x-rays, patient is exposed to ionising radiation which can potentially have long-term effect of inducing cancer [4]. The risk depends upon the age of the patient (greater at younger age), region and length of body scanned, and generation of CT scanner. The radiation dose can vary from 2 to 5 mSv for a cardiac CT on newer 128–320-slice scanner.

Magnetic Resonance Imaging (MRI)

MRI utilises the signal from spinning motion of the free hydrogen protons in the body tissues in a magnetic field when exposed to different radiofrequency waves and gradient fields to produces images [5]. The magnetic field is produced by either a permanent or superconducting magnet with the latter generally used for cardiac imaging with field strength of 1–3 T.

Images produced with MRI demonstrate various tissues with different 'signal intensity' (SI, compared to 'density' in CT) based on their T1 and T2 relaxation times which are inherent property of different tissues based on hydrogen proton concentration. The MRI images which predominantly demonstrate T1 characteristics of the tissues are called T1-weighted while those that demonstrate T2 characteristics are called T2-weighted. On T1-weighted images, tissues such as clear water (transudates, CSF, etc.), oedema, air, cortical bone, calcification, fibrosis have a low SI, soft tissues including myocardium, other muscles, and soft tissue tumours have intermediate SI, while fat and meth-haemoglobin have bright SI. On T2-weighted images, clear water, oedema, and tumour tissue would become bright, fat would be less bright, while air and cortical bone would continue to have low SI.

Cardiac MRI (CMR) imaging is typically performed with ECG-gating using different sequences for assessing the anatomy and function. Additional sequences can be performed in patients to demonstrate myocardial oedema (in those after acute myocardial infarction or myocarditis) and flow through aorta and main pulmonary artery without requiring any contrast. Sequences with contrast can be used to demonstrate ischaemia and infarction (for viability assessment). MR angiography can also be performed both with or without contrast.

The images with MRI can be obtained in any plane with cardiac images typically acquired in short- and long-axis (Fig. 4.1e–h) apart from orthogonal planes. A cardiac MRI scan typically takes between 40 and 60 min to perform.

The contrast used for MRI are chelates of gadolinium molecule but have similar pharmacokinetic properties to iodinated contrast media used in CT and catheter angiography. The allergic reactions are rare. Caution must be borne in patients with severe renal impairment (eGFR <35 ml/m^2) where there is a risk of developing nephrogenic systemic fibrosis.

Patients with pacemakers and other cardiac devices have traditionally been a contraindication for MRI scanning. However, there is growing evidence that MRI scanning can be safely performed in patient with conventional pacemakers with appropriate electrophysiology back-up and reprogramming [6]. Vendors have also developed MRI 'conditional' or safe devices which allow patients to undergo the scan safely [7]. Patients can safely be scanned after 4-weeks of any vascular stent insertion, cardiac bypass or valve surgeries. Presently, non-cardiac implantable programmable devices such as neurostimulators, insulin pumps, cochlear implants or intra-ocular foreign bodies remain a contraindication for MRI scanning.

The main technical differences between CT and MRI are given in Table 4.1.

Table 4.1 Essential differences between CT and MRI technology

	CT	MRI
Underlying technology	X-rays and detectors	Magnetic field and gradient coils
Tissue differentiation	Based on density	Based on signal-intensity produced by decay of radio-frequency pulses
Time taken for cardiac scan	5–15 min	40–60 min
ECG-gating for heart	Yes	Yes
Spatial resolution	0.3–0.6 mm	2–10 mm
Temporal resolution	60–200 s	30–60 s
Image plane	Axial but volumetric	Any plane
Contrast used	Iodinated low-osmolar	Gadolinium chelates
Ionising radiation (cardiac angiogram)	2–5 mSv with 128 to 320-slice scanner	Not applicable
Scanning in patients with pacemakers and other devices	Routinely possible	Relatively contraindicated[a]
Scanning in patients with stents, bypass surgery, prosthetic valves, and endovascular grafts	Routinely possible	Possible after 4–6 weeks

[a] MRI-conditional pacemakers are now available and routinely used in certain centres. However, there is now substantial data demonstrating safe use of conventional pacemakers in MRI provided certain precautions are taken

Clinical Applications of CT and MRI

By the time patients are referred to a cardiac surgeon, they have often undergone a full non-invasive assessment with one or more imaging techniques as well an invasive catheter angiogram (ICA). Latter supplemented with stress imaging or fractional flow reserve (FFR) is the current gold-standard for considering patient for coronary artery bypass grafting (CABG). However, it is important for surgeons to understand the role of both cardiac CT and MRI in evaluation of coronary artery disease (CAD) as part of pre-operative assessment as well as post-operatively. Similarly, both techniques play an important complimentary role in assessment of ventricular chambers, function, myocardium, valves, pericardium, great vessels and surrounding thoracic abnormalities. The main differences in applications of cardiac CT and MRI are shown in Table 4.2.

Coronary Artery Disease

Coronary artery disease is best demonstrated non-invasively with ECG-gated CT cardiac angiography (CTCA) which not only evaluates the degree of luminal stenosis but also shows calcified and non-calcified plaques in the wall of the coronary arteries (Fig. 4.2). CTCA is currently the most accurate non-invasive technique with high diagnostic accuracy (sensitivity of 90% and negative predictive value (NPV) of 99%) when compared to catheter angiography [8]. It has thus become the first imaging of choice for patients presenting with stable chest pain to exclude significant coronary artery disease [9, 10]. Patients with severe stenosis (≥70% diameter stenosis) on CTCA are referred for ICA to confirm the diagnosis and suggest suitability for percutaneous intervention (PCI) or CABG while those with moderate (50–69%) stenosis need a functional test to assess significant ischaemia.

CTCA is excellent for anatomical demonstration of left main stem and three-vessel disease. It is also useful to demonstrate the patency of distal LAD beyond total occlusion if not visible on ICA [11].

In the same examination, CTCA also demonstrates the size of the cardiac chambers (Fig. 4.1a–d), myocardial thickness, chronic infarction, morphology of the valves, pericardium, surrounding lung parenchyma, and the pleura. As most CTCA examinations are prospectively gated in mid-diastolic phase (70–80%) of cardiac cycle for best demonstration of coronary arteries, ventricular and valvular function cannot be assessed unless examination is requested and performed to include the entire cardiac cycle.

Table 4.2 Main differences in the clinical applications of cardiac CT angiogram and magnetic resonance imaging (MRI)

	Cardiac CTA	Cardiac MRI
Coronary arteries		
Atherosclerotic disease	+++	+
Patency of distal artery beyond occlusion	+++	+
Myocardial ischaemia	+++ (perfusion with vasodilator or dobutamine stress)	++ (perfusion with vasodilator stress or FFR-CT)
Ventricular function	+++	++ (requires retrospective ECG-gating)
Myocardial viability	+++	+
Cardiomyopathies	+++ (myocardial tissue characterisation)	+
Valvular diseases		
Stenosis	++ (demonstrates area)	+++ (demonstrates calcium and area)
Regurgitation	+++ (allows accurate quantification)	+ (by assessment of regurgitant area)
Congenital heart disease		
Coronary artery	+++	+
Left-to-right shunts	+++	++ (for anatomy only)
Right-to-left shunts	+++	++ (for anatomy only)
Aortic, venous, and pulmonary arterial anomalies	+++	+++
Pericardium		
Pericardial thickness & inflammation	+++	+++
Pericardial effusions	+++	+++
Pericardial calcification	+++	+
Pericardial constriction	++	+++
Cysts & tumours	+++	+++
Cardiac masses	++	+++
Aortic diseases		
Aneurysm	+++	+++
Acute aortic syndrome	+++	+
Post-surgical complications	+++	+

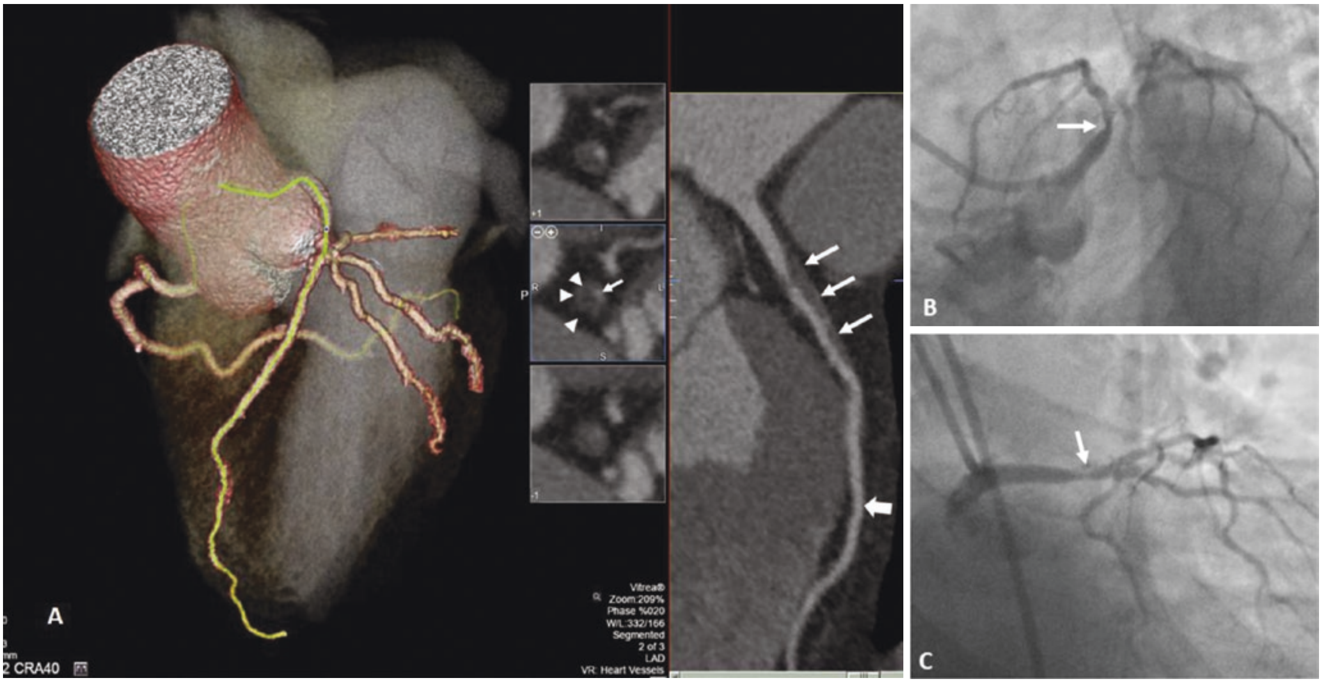


Fig. 4.2 Curved MPR from CTCA (**a**) of a 56 year-old man showing soft plaque in long-axis (arrows) images extending from the distal left main to proximal LAD and good calibre patent distal lumen (wide arrow). Accompanying short-axis image showing the eccentric plaque in the wall (arrow-heads) causing severe stenosis (lumen, arrow). Corresponding catheter angiogram (**b** and **c**) confirming the severe stenosis (arrows). *MPR* multi-planar reformat, *LAD* left anterior descending artery

CTCA can also be used to exclude significant CAD in patients presenting with acute chest pain with normal cardiac enzymes and no ST/T wave changes [12]. This can also exclude acute type-A aortic dissection with same scan, or if pulmonary embolism is to be excluded, a triple rule-out CTCA can be performed.

CT with or without ECG-gating can also be used to demonstrate the patency of the subclavian arteries and internal mammary arteries if required (Fig. 4.11a). It also allows assessment of the wall of ascending aorta for any calcification for on-pump surgery.

Cardiac MRI has a limited role in direct evaluation of CAD except by assessment of ischaemia as described below.

Myocardial Ischaemia

Cardiac MRI: Stress imaging with CMR has now emerged as an accurate non-invasive technique for assessment of myocardial ischaemia when compared with nuclear stress imaging and invasive FFR. The main advantage of CMR is lack of non-ionising radiation and comprehensive assessment of ventricular function, valves, and myocardial viability at the same time. A recent meta-analysis demonstrated a patient- and artery-based sensitivity, specificity, and a negative likelihood ration of 89%, 87%, and 0.12 respectively when compared to FFR [13].

Stress CMR is performed with pharmacological stress either using vasodilator agents such as adenosine or regadenoson (contraindicated in patients with asthma and second or third degree atrioventricular block) or chronotropic agents such as dobutamine. Intravenous gadolinium contrast is given at peak stress to assess the myocardial perfusion. Stress CMR images with vasodilator agents show hypoperfusion of the myocardium which reverses on rest (Fig. 4.3) and is considered to represent myocardial perfusion reserve compared to coronary flow reserve obtained with FFR. On the other hand, stress CMR with dobutamine would demonstrate areas of abnormal wall motion at peak stress becoming normal on rest.

Limited data suggests that CMR stress perfusion defect in ≥2 segments or a dobutamine-induced dysfunction in ≥3 segments (using 16-segment model) represents moderate to high risk (about 5% per year) for myocardial infarction or cardiovascular death, making these patients more suitable for revascularisation [14].

All non-invasive stress imaging techniques are limited in the demonstration of ischaemia in the present of severe anatomical left main or 3-vessel disease due to the phenomenon of balanced ischaemia. This remains true for stress CMR as

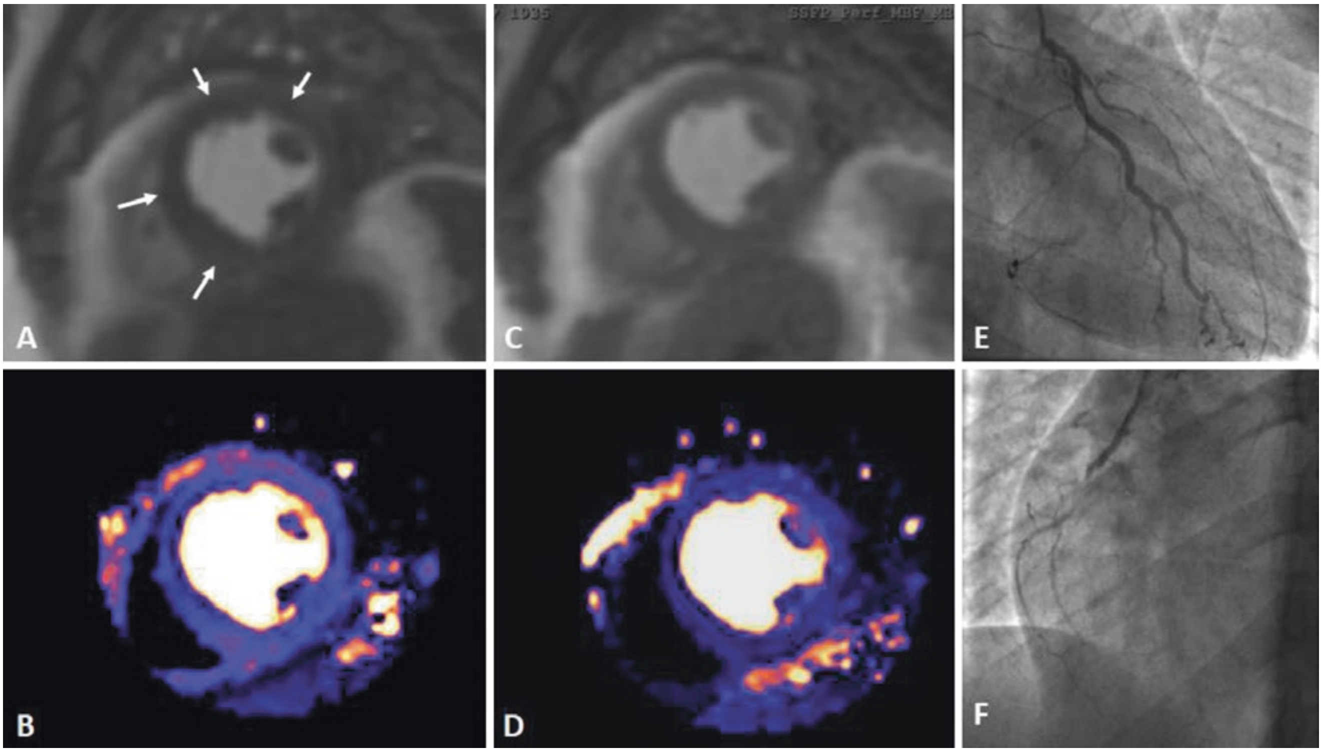


Fig. 4.3 Cardiac MRI with stress perfusion image (**a** and **b**) showing almost global reduced enhancement in the left ventricular myocardium (arrows) with normal perfusion on rest images (**c** and **d**). Corresponding catheter angiogram images (**e** and **f**) demonstrates severe three-vessel disease

well which show reduced specificity and negative predictive value in patients with 3-vessel disease [15].

Cardiac CTA: CTCA provides best anatomical assessment of coronary lumen and plaque burden but can also be combined with pharmacological stress in a similar way to CMR-SP to demonstrate myocardial ischaemia [16]. When compared to FFR, the accuracy of both techniques has been shown to be similar with sensitivity, specificity, positive and negative predictive value of 89%, 83%, 80%, and 90% [17]. Advantage of CTCA stress would be that both anatomical and functional assessment can be performed at the same examination with the limitation of additional radiation dose (5–10 mSv).

A more recent development has been to obtain FFR from anatomical CTCA images (FFR-CT) from the same images as used for delineation of the coronary arteries using computational fluid dynamics. Number of multicentre trials have shown that FFR-CT results in improvement in specificity and positive predictive value compared to just CTCA [18].

Myocardial Viability

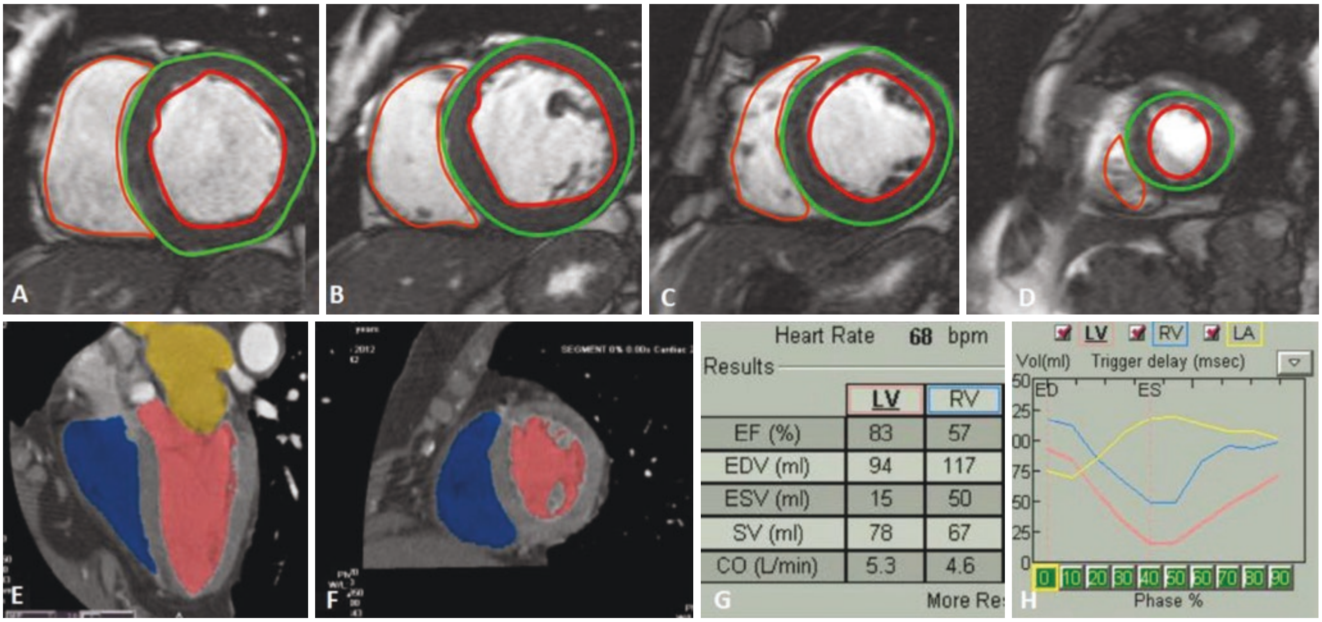
Cardiac MRI has become one of the most frequently used techniques for assessment of myocardial viability prior to revascularisation. Further use of imaging techniques for viability is described in another chapter.

Heart Failure and Cardiomyopathies

Cardiac MRI: Although echocardiography is routinely used as the first line investigation to assess cardiac function, cardiac MRI is more accurate for assessment of ventricular volumes and systolic function due to its superior delineation of endocardial border and less inter-observer variability [19–21] (Fig. 4.4a–d). CMR is recommended where echocardiography is non-diagnostic and/ or aetiology of heart failure is to be ascertained prior to surgical intervention. Ventricular volumes are typically calculated on CMR by delineating the endocardial border of series of short-axis views covering the entire ventricles in end-diastolic and end-systolic phases. Delineation of epicardial volume and subtracting it from the endocardial volume allows accurate calculation of myocardial mass.

Where available, CMR is now used routinely to assess heart failure due to ischaemic heart disease (Fig. 4.5a, b), cardiomyopathies such as dilated cardiomyopathy (DCM) (Fig. 4.5c, d) and hypertrophic cardiomyopathy (HCM) (Fig. 4.5e–h), restrictive cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, and infiltrative disorders of the myocardium like amyloidosis, Anderson-Fabry disease, etc.

Aetiology of heart failure or type of cardiomyopathy on CMR is determined by size and function of the cardiac chambers, myocardial thickness, and presence or absence of regional wall motion abnormality, valvular abnormality,



Heart Rate **68** bpm

Results

	LV	RV
EF (%)	83	57
EDV (ml)	94	117
ESV (ml)	15	50
SV (ml)	78	67
CO (L/min)	5.3	4.6

More Re

Fig. 4.4 Cardiac MRI images (**a**–**d**) in short-axis plane demonstrating semi-automated outlining of endocardial borders of both left and right ventricles which give the area of lumen in each short-axis which are used to determine the end-diastolic and end-systolic volume, stroke volume, and ejection fraction. The epicardial contours are used to calculate the epicardial volume which subtracted from endocardial volume give the myocardial volume and mass. CT cardiac angiography images (**e** and **f**) shows volumetric delineation of chamber lumen, volumes and systolic function (**g**) and time-volume curves (**h**)

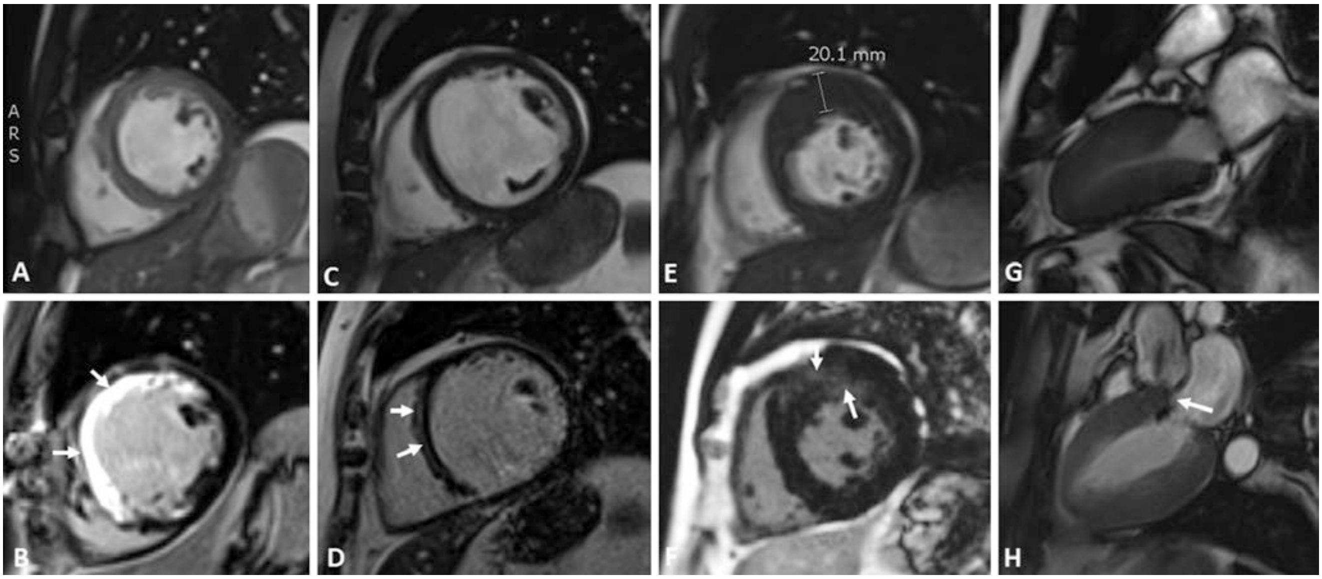


Fig. 4.5 Cardiac MRI images demonstrating patient with dilated left ventricle (**a**) with transmural delayed enhancement in the anterior wall and septum (**b**, arrows) suggestive of infarction. Another patient with idiopathic dilated cardiomyopathy showing mid-myocardial LGE (arrows). Images in a patient with hypertrophic cardiomyopathy showing asymmetrical hypertrophy of basal anterior wall and anterior septum (**e**) with LGE (**f**, arrows). Image **g** shows diffuse hypertrophy obliterating the LV cavity in end-systolic phase and **h** shows LV outflow tract obstruction (arrows)

pericardium and delayed gadolinium enhancement (DGE). Distribution and pattern of DGE allows one to differentiate between infarction and fibrosis from other causes such as DCM and HCM. More recently, parametric mapping with native T1, T2, T2∗, and extracellular volume has been shown to characterise both focal and diffuse myocardial diseases and should be considered in CMR evaluation in patient with heart failure [22]. Patients with extensive myocardial fibrosis either of ischaemic or non-ischaemic aetiology or specific cardiomyopathy (except HCM for myomectomy) have shown to be of greater risk and may not be suitable candidates for surgery.

Cardiac CT: The best role of CTCA in patients with new onset heart failure is in demonstration or exclusion of coronary artery disease as the underlying cause [19]. If performed to include the end-diastolic and end-systolic phases of cardiac cycle, CTCA can also quantify ventricular volumes and myocardial mass using 3-D volumetric technique due to high-resolution volumetric acquisition compared to CMR [23] (Fig. 4.4e–h). Like CMR, DGE can also be performed with CTCA, but at the cost of increased radiation dose and contrast. It is thus advisable only in patients where CMR is contraindicated.

Valvular Heart Disease

Cardiac MRI: CMR is complementary to echocardiography in the assessment of valvular heart disease [24]. CMR can demonstrate the morphology of all the cardiac valves and help in quantifying the degree of stenosis and regurgitation apart from assessing the size and function of the cardiac chambers [21, 25]. Degree of myocardial fibrosis can also be assessed as described above. This can also help in differentiating primary from secondary valve abnormality.

The degree of stenosis is quantified by simple planimetry of valve orifice and calculating the minimal valve area at its maximal opening. Maximum flow velocity and gradients can also be quantified with CMR but are less reliable compared to echocardiography.

However, the greatest utility of CMR is perhaps in the quantification of valvular regurgitation, particularly that of aortic and mitral valve [25]. This is best obtained by performing phase contrast flow mapping through the aortic root which provides the amount of antegrade flow volume to the ascending aorta and any retrograde regurgitant flow (aortic regurgitation) (Fig. 4.6a–d). Mitral regurgitant volume is obtained by subtracting the antegrade flow volume from the LV stroke volume.

Cardiac CT: CTCA also demonstrates the morphology well due to high spatial resolution and presence of contrast in the cardiac chambers across the valves [26]. CT is best for demonstration of calcification in the valves and surrounding annulus. In patients with aortic stenosis, calcification is increasingly being used to confirm the severity of AS particularly in low-flow low-gradient stenosis (Fig. 4.6e). The aortic as well as mitral valve area can be easily obtained by direct planimetry of the valve orifice if the imaging has been performed through the relevant phase of cardiac cycle (Fig. 4.6f).

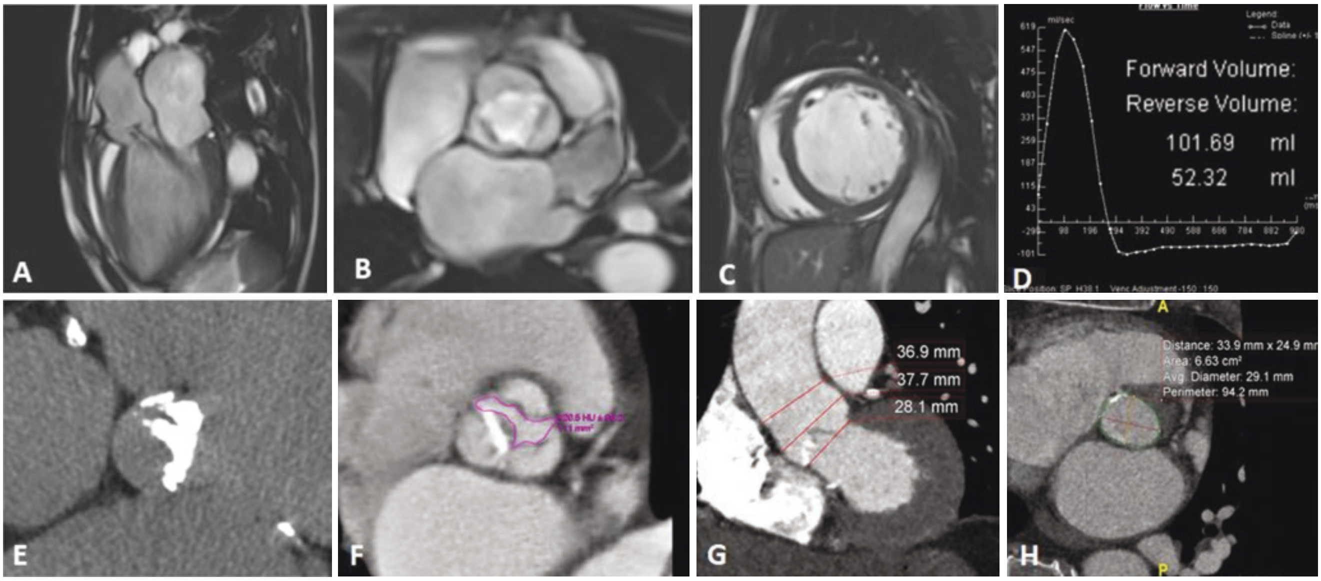


Fig. 4.6 Cardiac MRI images of a patient demonstrating aortic valve regurgitation in left ventricular outflow tract view (**a**), an open tricuspid valve (**b**), and dilated left ventricle (**c**). The flow-time curve (**d**) from phase-contrast sequence through aortic root shows substantial flow of blood in diastolic phase (below the X-axis) which can be quantified. CTCA images show severe calcification in the aortic valve (**e**) with an orifice area of 1.1 on direct planimetry (**f**). CTCA allows accurate measurements of aortic root and annulus (**g** and **h**)

CTCA is now become the main imaging modality for TAVI (transcatheter aortic valve implantation) for assessment of size of aortic root including the annulus (Fig. 4.6g, h), and the peripheral access [27]. The technique can similarly be used to assess the same for minimally invasive aortic and mitral valve surgery for assessment of annulus size, calcification, distance from the surrounding arteries and chest wall [28]. CTCA also allows assessment of the surrounding lung parenchyma and thoracic aorta.

Congenital Heart Disease

Both CTCA and CMR are excellent in demonstrating the anatomy of the cardiac chambers and great vessels in any congenital cardiac or vascular abnormality. The average age of patients with CHD is shifting upwards due to reduced mortality with two-third patients being adults. This allows easier performance of follow-up imaging with CTCA and CMR over the adult life.

The advantage of CTCA would be a quick volumetric acquisition compared to CMR, particularly with wide detector scanners that can scan whole heart in single rotation or using fast pitch, thus obviating the need for sedation or general anaesthesia in younger children [29]. The main limitation of CTCA would be its inability to quantify function (unless retrospective gating is utilised) and flow and exposure to ionising radiation.

CTCA is best for demonstrating the anomalies of the coronary arteries, coronary fistulas, Kawasaki disease, and after surgical repair requiring coronary artery manipulation [29]. It is well suited to demonstrate congenital anomalies of the thoracic aorta including coarctation and their post-intervention follow-up, pulmonary artery, and systemic and pulmonary veins. CTCA may be helpful in further anatomical delineation of left to right shunts and associated anomalies as well as in patients with Tetralogy of Fallot.

The strength of CMR is in estimating the shunt by measuring flow through the ascending aorta and main pulmonary artery using the phase-contrast technique as described above and quantifying function of the ventricles [30]. CMR is also the technique of choice for following up patients after surgical repair.

Pericardial Diseases

The anatomy of the pericardium and surrounding layers of fat is well delineated on both CTCA and CMR [31]. Both techniques can demonstrate thickened pericardium and any inflammatory changes in pericarditis (Fig. 4.7a, b). CT is best for demonstrating calcification in the pericardium and its extent along with any fibrosis in the surrounding lung parenchyma which may occur in patients with previous radiotherapy (Fig. 4.7c, d). Pericardial effusion can also be well demonstrated on both techniques which can also help in characterising the composition of fluid as transudate or exudate (Fig. 4.7e, f).

As CMR is helpful in evaluating ventricular function, it can easily demonstrate any septal bounce in patients with suspected constrictive pericarditis. Both techniques are helpful in evaluating congenital pericardial cysts and masses. CMR can also assess any myocardial involvement with pericardial or para-cardiac tumours using cine sequences.

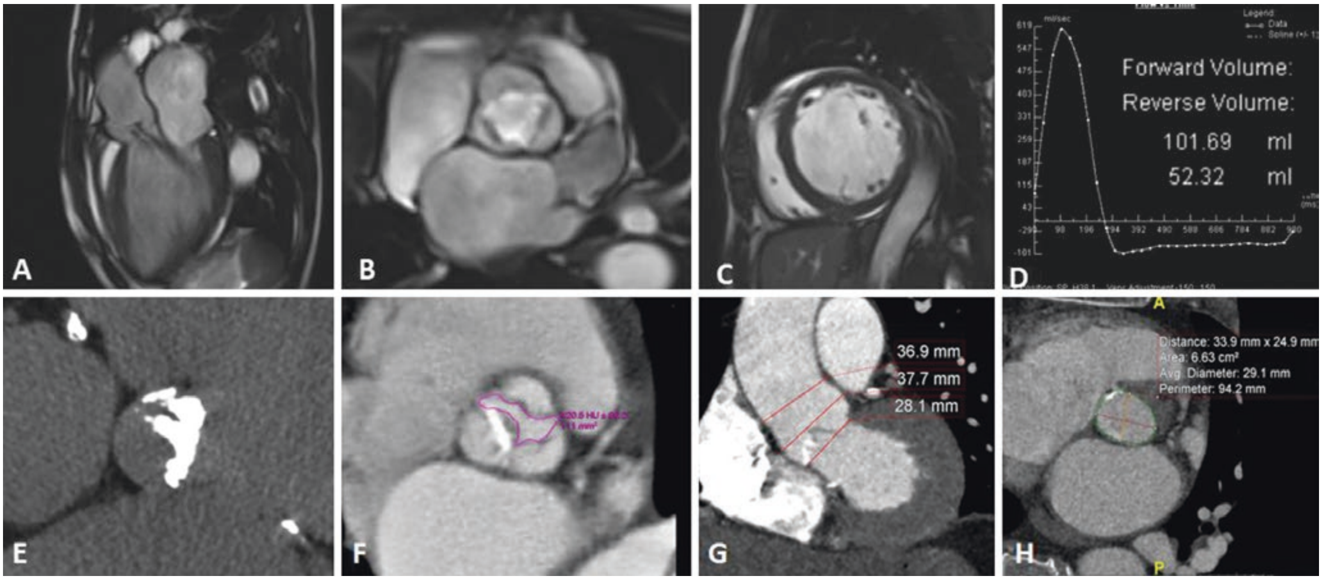


Fig. 4.7 Diffuse thickening of the pericardium on CTCA (**a**) and CMR (**b**). Extensive calcification of pericardium on 4-chamber view (**c**, arrows) and 3-dimensional (**d**, asterisk). Pericardial effusion on CTCA (**e**, arrows) and on CMR (arrows). CMR image showing a localised tumour on the inferior aspect of left ventricle while H shows extensive soft tissue mass involving myocardium and pericardium (arrows). *CTCA* CT cardiac angiogram, *CMR* cardiac MRI

Cardiac Tumours

Although metastatic masses are commonest tumours involving the heart and pericardium, they would not present to a surgeon except perhaps for a biopsy. The commonest tumours in surgical practice are the myxomas, which are benign tumours mostly found in the left atrium. Diagnosis is usually made on echocardiography which may be the only imaging test required for surgical referral. However, left atrial tumours with unusual characteristics (such as fixity to the posterior wall) or cardiac masses require further assessment with CTCA and/ or CMR which have the benefit of a larger field of view.

Both techniques provide valuable information about the morphology, location, extent, and tissue characteristics of tumours and masses involving the heart [32] (Fig. 4.7g, h). CT in addition is more robust in identifying pulmonary and other abnormalities including primary tumours elsewhere and is much faster to perform compared to MRI. PET (Positron Emission Tomography) with 18F-FDG now complements CT in identifying active tracer uptake in the abnormal pericardium/ cardiac mass and elsewhere in the body that may represent primary or secondary neoplastic tissue.

Benign tumours appear as well defined localised soft tissue masses (Fig. 4.7g) while malignant ones as infiltrating or invasive masses (Fig. 4.7h). Malignant tumours can also demonstrate invasion through the myocardium and pericardium into surrounding lung or mediastinum along with complex or haemorrhagic pericardial effusion. The density or signal intensity of the tumour could be characteristic of their predominant tissue component and may show varying degree of enhancement with contrast on both CT and MRI. Cine MRI can be used to identify involvement of underlying myocardium by a pericardial tumour and help in surgical resection.

Aortic Diseases

Both CT and MRI are crucial in diagnosis and management of aortic diseases including thoracic and abdominal aortic aneurysms and acute aortic syndrome (AAS) [33]. CT is best performed with ECG-gating particularly for accurate measurement of size of ascending aorta and aortic root and exclusion of dissection flap due to motion artifacts from the heart. Intravenous contrast is administered to demonstrate the aortic lumen although a pre-contrast scan can be useful to demonstrate intra-mural haematoma when AAS is suspected.

Both techniques provide information about the size and extent of aortic dilatation, involvement of aortic root, branches of the arch and abdominal aorta. Although both demonstrate atherosclerosis in the aortic wall, CT is superior in demonstrating calcification. It is important that the size of the aorta or root is always measured perpendicular of the long-axis or direction of blood flow using multi-planar reconstructions (Fig. 4.8). The aortic size can also differ depending upon the phase of cardiac cycle and if measurement is performed from inner to inner wall, inner to leading wall, or outer to outer-wall. As there is no consensus on these aspects, for follow-up studies, a side-by-side comparison and measurements should be performed in the same plane, preferably using the same imaging technique. An increase in size by 5 mm or more in follow-up study is taken as significant considering inter- and intra-observer variability [33]. MRI has the advantage for follow-up studies due to lack of ionising radiation particularly in younger patients.

CT when performed with ECG-gating is the best modality to assess the aorta in patients with suspected AAS. It demonstrates the extent of dissection flap and any tears (Fig. 4.9), extension of flap in branches of aortic arch and abdominal aorta, involvement of coronary arteries, pericardial haemorrhage, and perfusion of visceral organs.

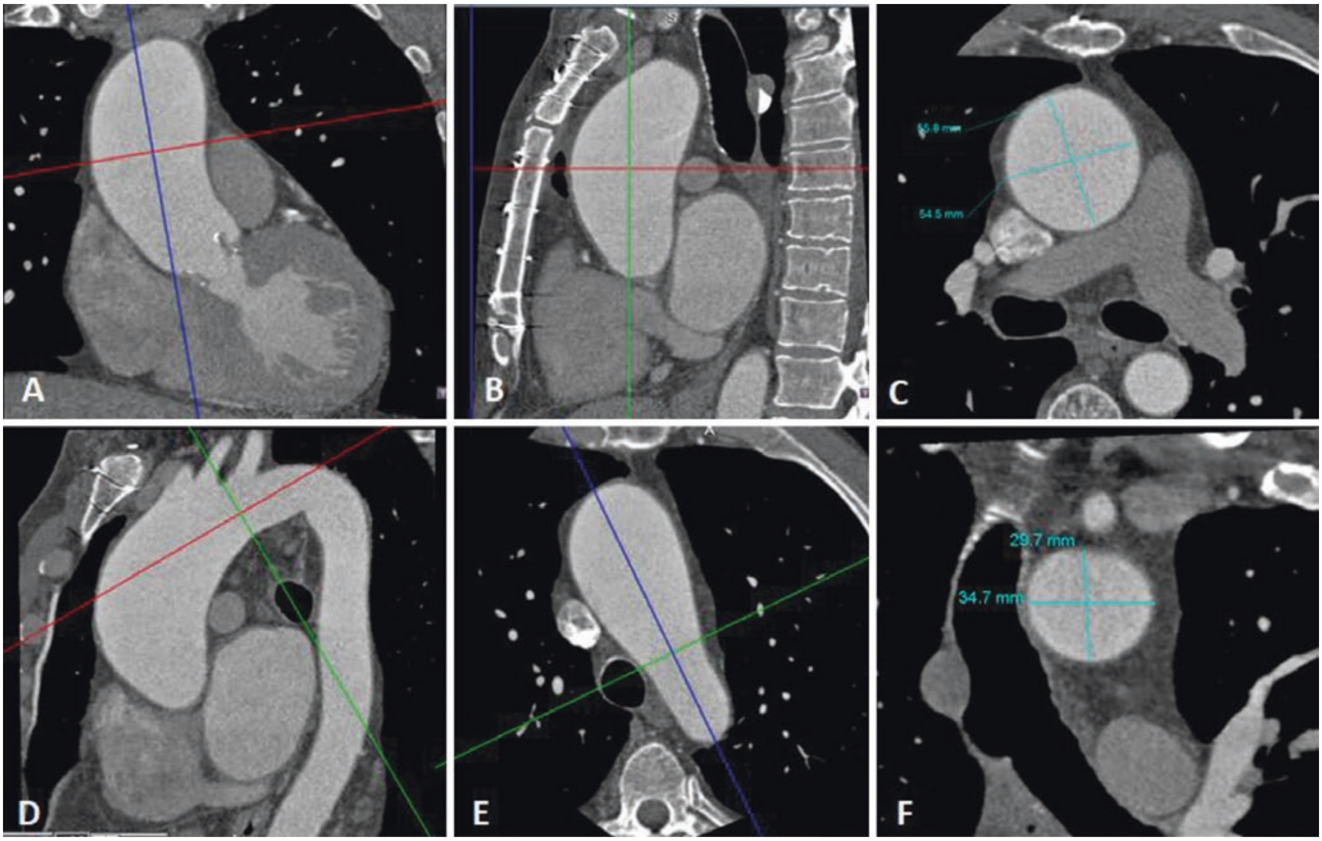


Fig. 4.8 Patient with fusiform aneurysm of ascending aorta. CT angiogram images demonstrating measurement of the maximum diameters of the aneurysm in a short-axis plane perpendicular to the long-axis of the ascending aorta from the coronal and sagittal oblique images (**a**-**c**). Similarly measurement of the mid aortic arch from the two oblique images (**d**–**f**)

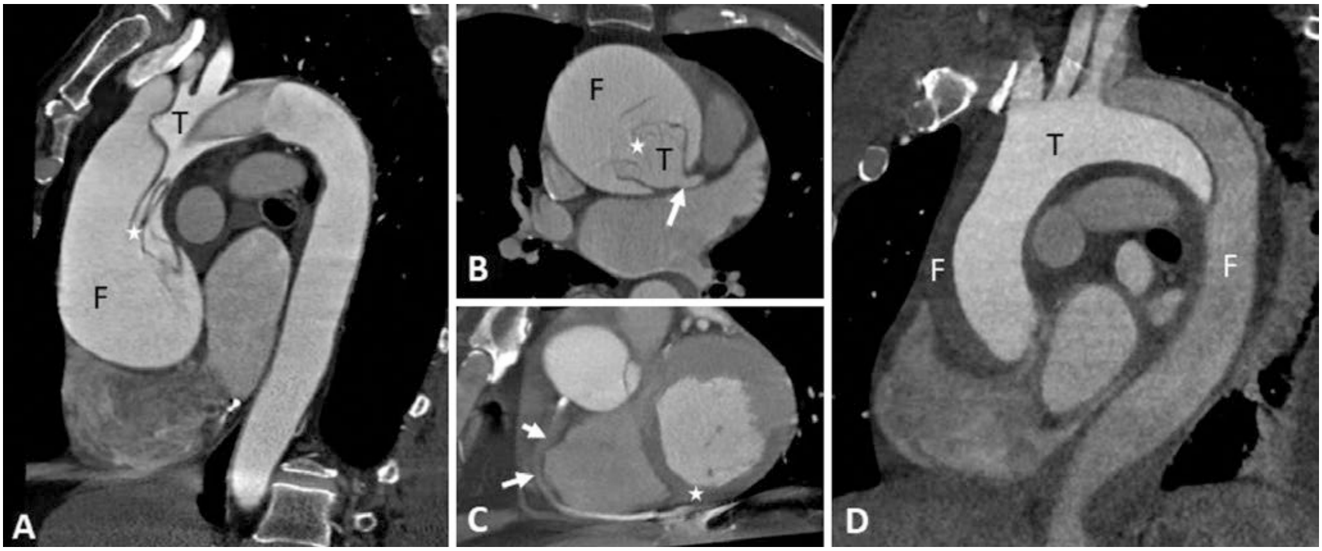


Fig. 4.9 CTCA images in patients with Type A aortic dissection with large patent false lumen (F) in **a** and **b** with multiple tears (asterisks). The left coronary artery (arrow) arises from the smaller true lumen (T) in image **b**. Image **c** shows occlusion of the right coronary artery with myocardial infarction (asterisk). Thrombosed false lumen in ascending aorta in image **d**

Post-surgical Patient

In patients with CABG, CTCA is useful to both identify the number and location of bypass grafts, and to assess their patency [34] (Fig. 4.10). When compared to ICA, CTCA has a sensitivity and specificity of CTCA of 97% and NPV of 99% for assessment of graft patency.

CT is well able to demonstrate any thrombosis of the prosthetic valves, peri-aortic abscess, complications related to replacement of aortic root and thoracic aorta such as haematoma, infective collections, pseudo-aneurysms (Fig. 4.11c, d), perforation, or rupture. MRI is less helpful in these situations. CT is routinely performed to assess presence or absence of retro-sternal collections.

In patients being planned for redo sternotomy, CT is also able to demonstrate the course of the bypass grafts and position of anterior surface of heart, aortic root, and ascending aorta with relation to the sternum (Fig. 4.11b).

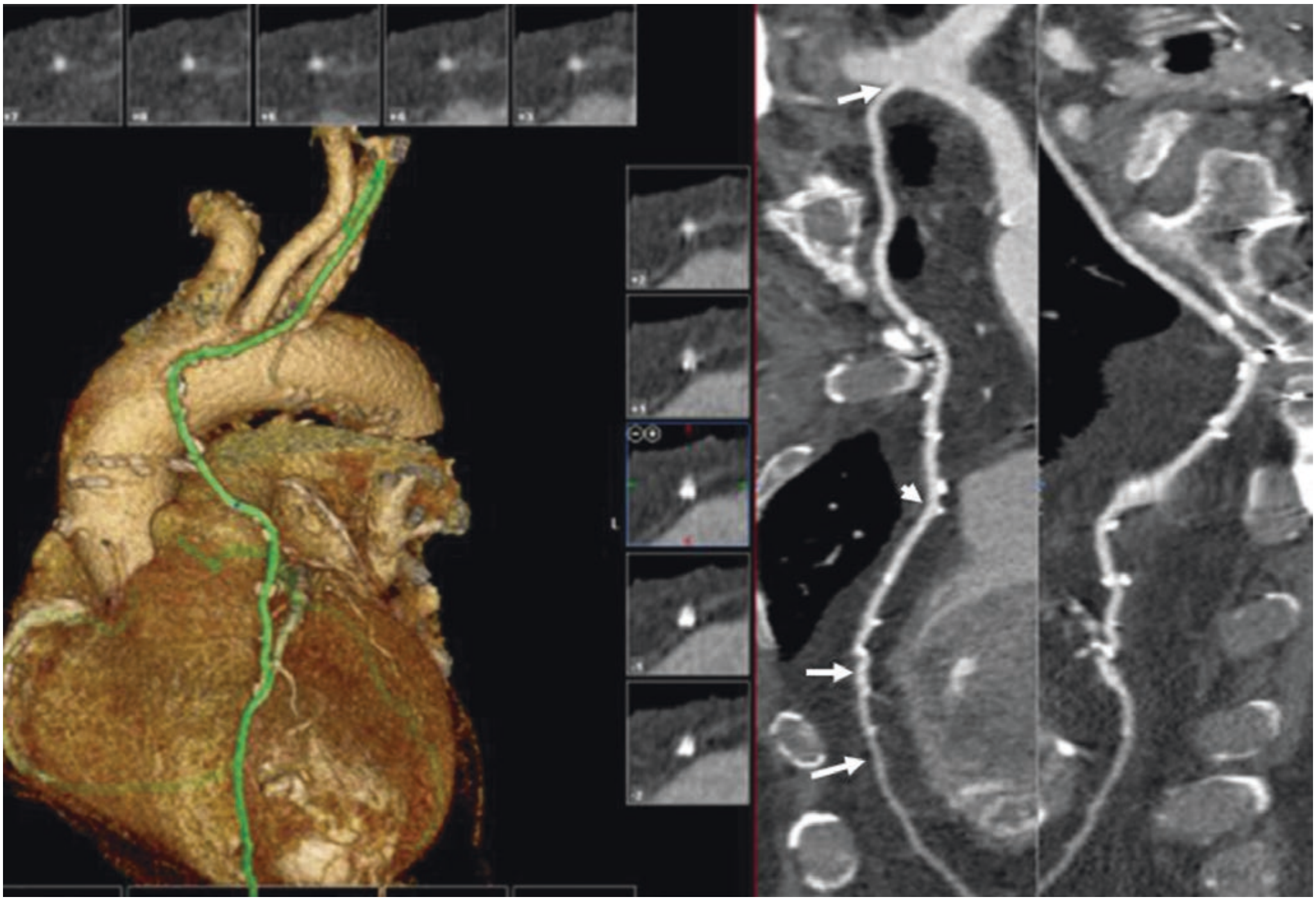


Fig. 4.10 CT cardiac angiogram showing left internal mammary graft (LIMA) as curved multi-planar reformat (MPR) image on the right and corresponding 3-d image on the left with the LIMA highlighted in green. The MPR demonstrates the lumen of LIMA from its origin (arrow) to the distal anastomosis (arrowhead) and further native distal artery (two arrows)

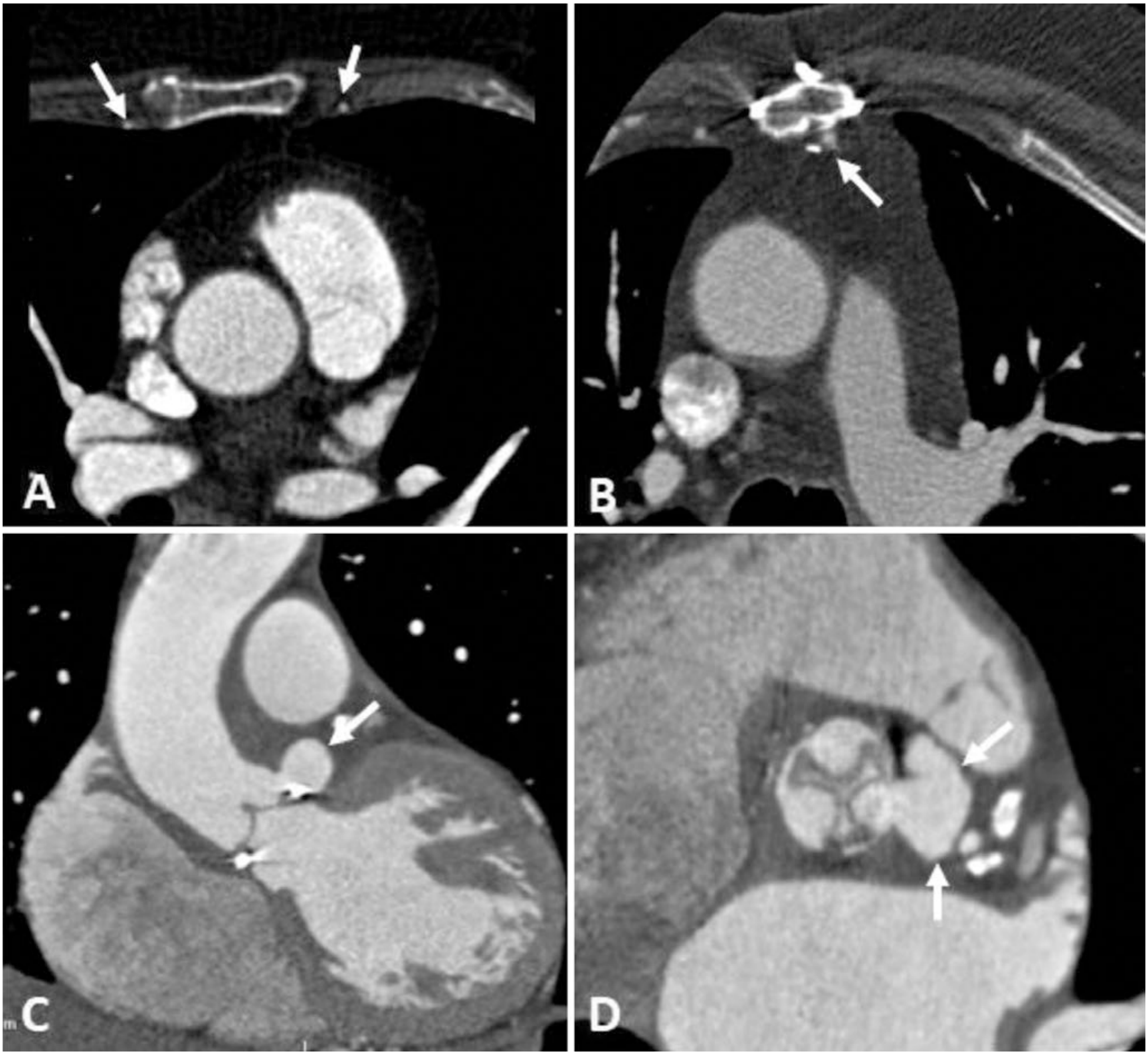


Fig. 4.11 CT cardiac angiogram images demonstrating the two internal mammary arteries in their normal positions (**a**, arrows), left internal mammary graft posterior to the sternum (**b**, arrows), and a pseudoaneurysm in a patient with previous bioprosthetic AVR in coronal (**c**, arrow) and short-axis (**d**, arrows) planes. *AVR* aortic valve replacement

Conclusion

Several cardiac imaging modalities have become essential in the practice of modern cardiovascular medicine not only in diagnosis but also in the management of various cardiovascular diseases as well as in the guidance of invasive procedures. Amongst these imaging modalities CT and MRI have transformed the evaluation and diagnosis of cardiovascular diseases. Each modality has its pros and cons and can be used individually or in combination depending on desired diagnostic needs.

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Assessment of Myocardial Viability

5

Chandra Katikireddy, Nareg Minaskeian, Amir Najafi, and Arang Samim

High Yield Facts

- Viable myocardium refers to dysfunctional myocardium that is expected to recover contractility following revascularization, resulting in improved left ventricular ejection fraction.
- Low dose dobutamine stress echocardiography and dobutamine stress CMR assess the contractile reserve of dysfunctional myocardium and possess high specificity and positive predictive value in diagnosing the myocardial viability.
- SPECT and PET nuclear techniques estimate myocardial perfusion and metabolic activity (^{18}F-FDG PET) to evaluate myocardial viability with a high sensitivity and negative predictive value.
- CMR late gadolinium enhancement (LGE) technique estimates myocardial scar burden accurately.
- Myocardial viability status in ischemic cardiomyopathy may have a prognostic and therapeutic utility with better outcomes in those with viable myocardium treated with optimal medical therapy and coronary revascularization when appropriate.
- In ischemic cardiomyopathy with viable myocardium, according to ACCF/AHA 2013 heart failure guidelines, it is a class IIA recommendation for coronary revascularization if LVEF >35% and class IIA recommendation for either medical therapy or revascularization when LVEF <35%

Introduction

Left ventricular systolic dysfunction as a result of coronary artery disease and ischemia portends a poor prognosis from heart failure and arrhythmias.

Hibernating myocardium is a viable, dysfunctional state of the myocardium with a persistently reduced contractility due to reduced coronary blood flow at rest, which may be partially or completely reversible upon revascularization [1]. Stunned myocardium is a dysfunctional state that may persist for a period of time after an episode of transient ischemia despite the restoration of normal blood flow, with spontaneous recovery subsequently [1, 2]. Chronic, repetitive stunning may lead to a hibernating state in myocardium in a short period of time [3]. Non-viable myocardium, as compared to the two former viable states, is the result of irreversible necrosis of the myocytes leading to fibrosis and infarction [1]. It is important to recognize that progression of untreated ischemia and eventual replacement of hibernating myocardium by fibrosis without therapy is a chronic, continuum process [1, 4]. In a chronic state of ischemia, hibernating myocardium can be at early, intermediate or late pre-fibrotic states and success of recovery with therapy and revascularization depends on the stage at which the therapeutic intervention is made.

The following sections provide an overview of assessment of myocardial viability, its therapeutic and prognostic implications as well as management of ischemic cardiomyopathy based on the myocardial viability status.

Assessment of Myocardial Viability

Myocardial dysfunction with impaired contractility is typically termed as ‘viable’ if it is predicted to recover contractility with medical therapy and coronary revascularization. Viability is estimated by different imaging modalities probing various characteristics of the viable myocardium: end diastolic

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wall thickness on echocardiography (Echo) or cardiac magnetic resonance (CMR), contractile reserve assessment with low dose dobutamine by Echo or CMR, cell membrane integrity based on radioactive tracer uptake on single positron emission computed tomography (SPECT), ischemic myocardial metabolic properties (cellular glucose uptake) by positron emission tomography (PET), and late gadolinium hyper-enhancement (scar) by CMR. Diagnostic accuracy of different imaging modalities in estimating viable status of myocardium is comparable. However, in general, tests (dobutamine Echo and CMR) that evaluate contractile reserve possess higher positive predictive value and specificity, but lower sensitivity compared to those that estimate myocardial perfusion, cell membrane integrity and metabolic properties (SPECT and PET, respectively) which are known to have higher negative predictive value and sensitivity but lower specificity to detect myocardial viability [3–6]. Of note, predominantly, the data comparing the diagnostic accuracy of different imaging tests were not performed in the same subjects.

Commonly used imaging modalities used for viability assessment in the clinical practice (Table 5.1) are described below.

Electrocardiogram (ECG)

The ECG is an initial and useful tool in the evaluation of viability. While the absence of pathologic Q waves may be suggestive of viable myocardium [7] the presence of Q waves is not specific for myocardial infarction. Myocardial hypertrophy, WPW and rarely hibernating myocardium [8] should be considered in the differential diagnoses of pathologic Q waves in addition to myocardial infarction. It would be prudent to consider the presence or absence of Q waves not in isolation but in conjunction with the other imaging markers of myocardial viability status.

Baseline 2D Echocardiography

Myocardial thickness may provide a clue to the viability status. Normal segmental thickness (>6 mm) implies viable myocardium and severely thinned (4 mm or less) segments may be suggestive of non-viable or terminal stages of hibernating myocardium. In a meta-analysis, intact end diastolic wall thickness showed a sensitivity >90% but low specificity of <50% in predicting contractile recovery with therapy [9].

Table 5.1 Comparison of imaging modalities for myocardial viability

Imaging modality	Viability assessment	Sensitivity	Specificity	Advantages	Limitations
DS Echocardiography	Demonstration of contractile reserve	Moderate (70–80%)	High (80–90%)	No radiation No iodinated contrast Quick Routinely available	Higher false-positive rate Moderate positive- predictive value
^{201}Tl MPI SPECT	Normal perfusion (>50% of a normal segment) on redistribution imaging	High (80–90%)	Low to moderate (59%)	Traditionally accepted modality	Time consuming Radiation risk Limited sensitivity
Tc-^{99m} MPI SPECT	Normal perfusion (>50% of a normal segment)	Moderate to high (80–90%)	Moderate (60–70%)	Quicker than ^{201}Tl redistribution imaging Myocardial ischemia and LV function assessed simultaneously	Unable to distinguish ‘nonviable’ from ‘hibernating’ myocardium, especially in nontransmural infarcts Radiation risk
^{82}Rb ^{18}F-FDG PET	Perfusion defect with intact metabolism	High (>90%)	Moderate (60–70%)	Superior diagnostic accuracy to SPECT imaging Less radiation Less time consuming	Unable to distinguish subendocardial from transmural infarcts Not routinely available
DS CMR	Presence of contractile reserve	Moderate to high (80%)	High (90%)	Accurately images myocardial scar Superior spatial resolution Differentiates subendocardial from transmural infarct No radiation	Limited outcome data
LGE CMR	Absence of LGE or < 50% transmural extent of LGE with presence of contractile reserve on DS CMR	Moderate to high (80–85%)	Moderate (60–70%)	Superior spatial resolution Less radiation	Hyperenhancement on LGE-CMR may be seen with myocardial necrosis, edema and inflammation

CMR Cardiac magnetic resonance, *DS* Dobutamine stress, *LGE* Late gadolinium enhancement; ^{82}*Rb* ^{18}*F-FDG PET* Rubidium, fluorine fluorodeoxyglucose positron emission tomography, ^{201}*Tl MPI SPECT* Thallium myocardial perfusion imaging single photon emission computed tomography

Dobutamine Stress Echocardiography

Stress echocardiography using dobutamine (Fig. 5.1) is a simple, low-risk, non-invasive test with no radiation risk. Myocardial contractile reserve is used as an indicator of viability [3]. Viable, dysfunctional myocardium with contractile reserve in a minimum of >5 segments, increases the success rate of functional recovery following coronary revascularization [10]. Hypokinetic or akinetic hibernating myocardium may demonstrate improved contractility with low dose dobutamine (5–10 μg/kg/min) infusion [1, 11]. At higher doses of dobutamine infusion, hibernating myocardial contractile function may worsen due to ischemia (biphasic response) or continue to improve with no evidence of ischemia. Biphasic response increases specificity (up to 84%) for viable hibernating myocardium [12]. On the contrary, lack of contractile reserve or no ischemic response at higher doses of dobutamine, decreases the specificity.

Single Photon Emission Computerized Tomography (SPECT)

In SPECT imaging, the radionuclide tracer uptake property of the viable cardiac myocyte with an intact cell membrane is used to estimate myocardial viability status. The initial myocardial uptake of 201 Tl (Thallium) is determined by early myocardial perfusion whereas the subsequent uptake over the next 24 h is determined by 'refill and redistribution' of the isotope, determined by the integrity of the cellular membrane [3]. Hibernating myocardium appears as a perfusion defect on early images due to impaired blood flow at baseline but normalizes (at least >50% radioactive tracer uptake of the normal segments) on delayed imaging from redistribution of the 201 Tl. Sensitivity of viability detection on 201 Tl imaging increases in late (24 h) reinjection/redistribution protocols compared to 4 h early redistribution protocol.

Tc^{99m} is dependent on a passive mitochondrial uptake with no redistribution property. When artefactual finding is excluded, perfusion defect at rest on Tc imaging can be either infarct or hibernating myocardium (Fig. 5.2). Further distinction of these fixed perfusion defects can be determined by the presence of wall motion, thickening, and worsening of perfusion defect with stress to some degree in the hibernating myocardium. Even though Tc is considered inferior to Tl imaging due to lack of redistribution feature, studies have shown that both are comparable in diagnostic accuracy of viable myocardial detection [1, 3]. The sensitivity and specificity of ^{201}Tl was demonstrated to be 86 and 59%, respectively, for predicting functional recovery after revascularization and 81 and 66% for Tc^{99m}, respectively [1]. Nitrate administration may increase the sensitivity of viability detection by SPECT.

Positron Emission Tomography (PET)

PET imaging uses the preserved metabolic property of viable myocardium as opposed to the absence of metabolic activity in scar. Superior resolution, quick imaging, absolute quantification of myocardial perfusion and less radiation exposure are the advantages of PET over the SPECT.

Cardiac PET uses Rubidium-82 (^{82}Rb) to assess perfusion and F18-Fluorodeoxyglucose (^{18}F-FDG) to assess myocardial glucose metabolism [1, 3, 4]. Viable myocardium is characterized with reduced perfusion and preserved ^{18}F-FDG up take (Fig. 5.3) [3]. Meta-analyses have indicated a superior diagnostic accuracy of PET in comparison to other modalities to detect viable myocardium [3].

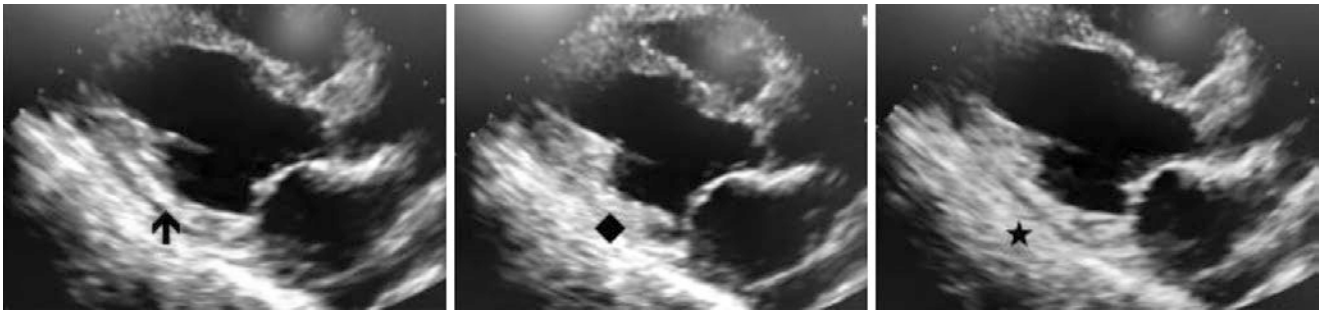

Fig. 5.1 Dobutamine stress Echocardiography demonstrating ischemia and viability (biphasic response) of the inferolateral wall. (**a**) Arrow: Hypokinesis in end systole at baseline; (**b**) Diamond: Improved motion and thickening in systole with low dose dobutamine; (**c**) Star: Hypokinesis at peak dose of dobutamine

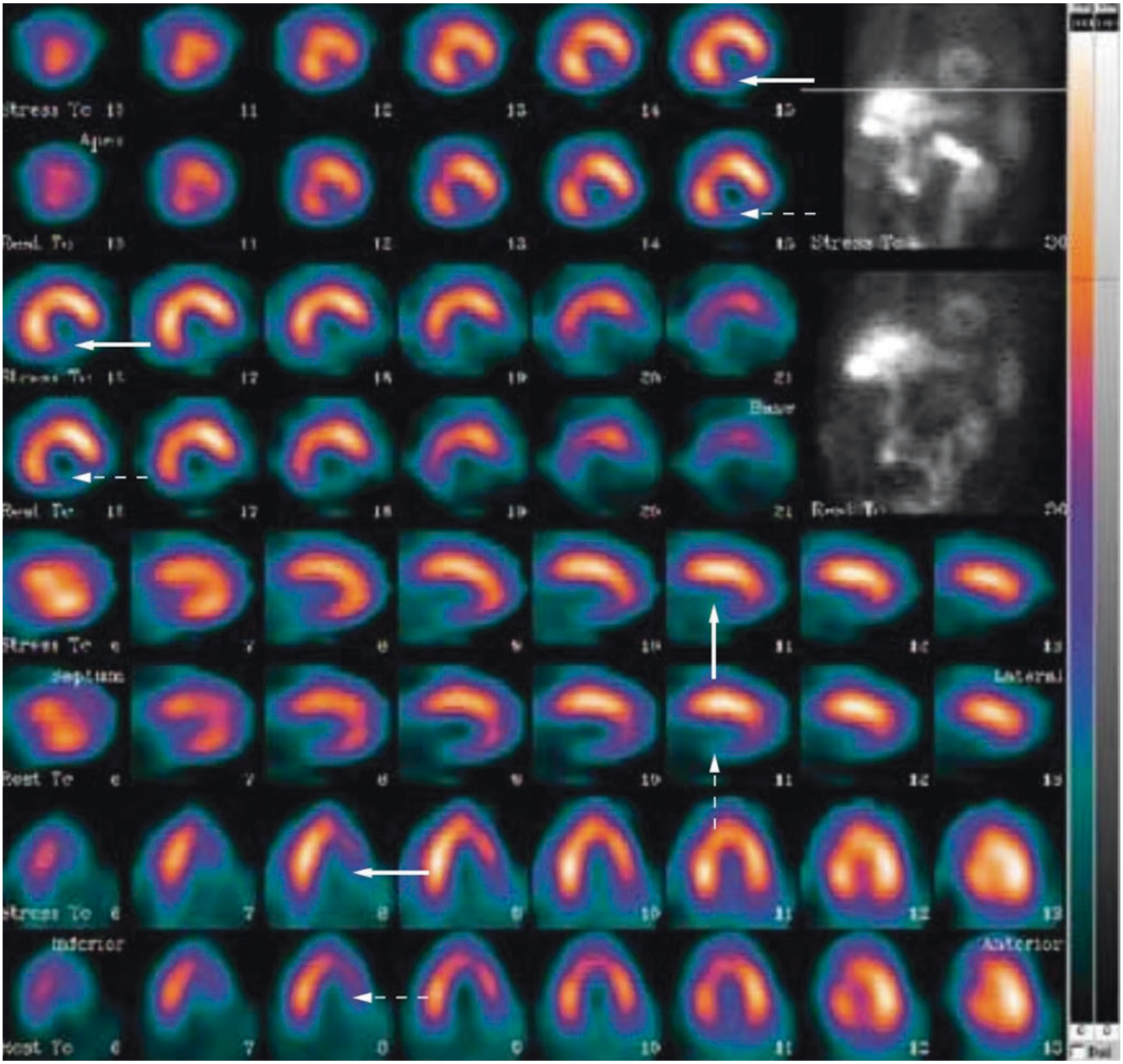

Fig. 5.2 Tc—SPECT imaging showing a fixed perfusion defect in stress (solid arrow) and rest (dashed arrow) imaging of the mid to basal, inferior and inferolateral wall—indicative of scarred, nonviable myocardium

Cardiac Magnetic Resonance Imaging (CMR)

CMR's ability to directly image and estimate the scar burden, myocardial perfusion, segmental wall motion, thickness and contractile reserve with dobutamine infusion, left ventricular ejection fraction, and ventricular volumes [3, 6], makes CMR an ideal test to evaluate myocardial viability in a comprehensive manner.

Gadolinium contrast is rapidly cleared from normal myocardium within 10 min. However, the contrast is trapped in the interstitial space of the scarred myocardium, delaying its clearance and appears bright and enhanced in late gadolinium enhancement (LGE) imaging [13]. Due to superior spatial resolution, CMR can accurately quantify the extent and transmurality of scar tissue and viable myocardium [1]. If transmurality of LGE of a myocardial segment is greater than 50% (Fig. 5.4), it is considered non-viable and is unlikely to recover following revascularization [1, 3, 6]. If LGE is <50% of segmental thickness, myocardium is likely viable, and the diagnostic accuracy of viability can be further enhanced by demonstrating contractile reserve with low dose dobutamine [3]. Integration of multiple viability markers;

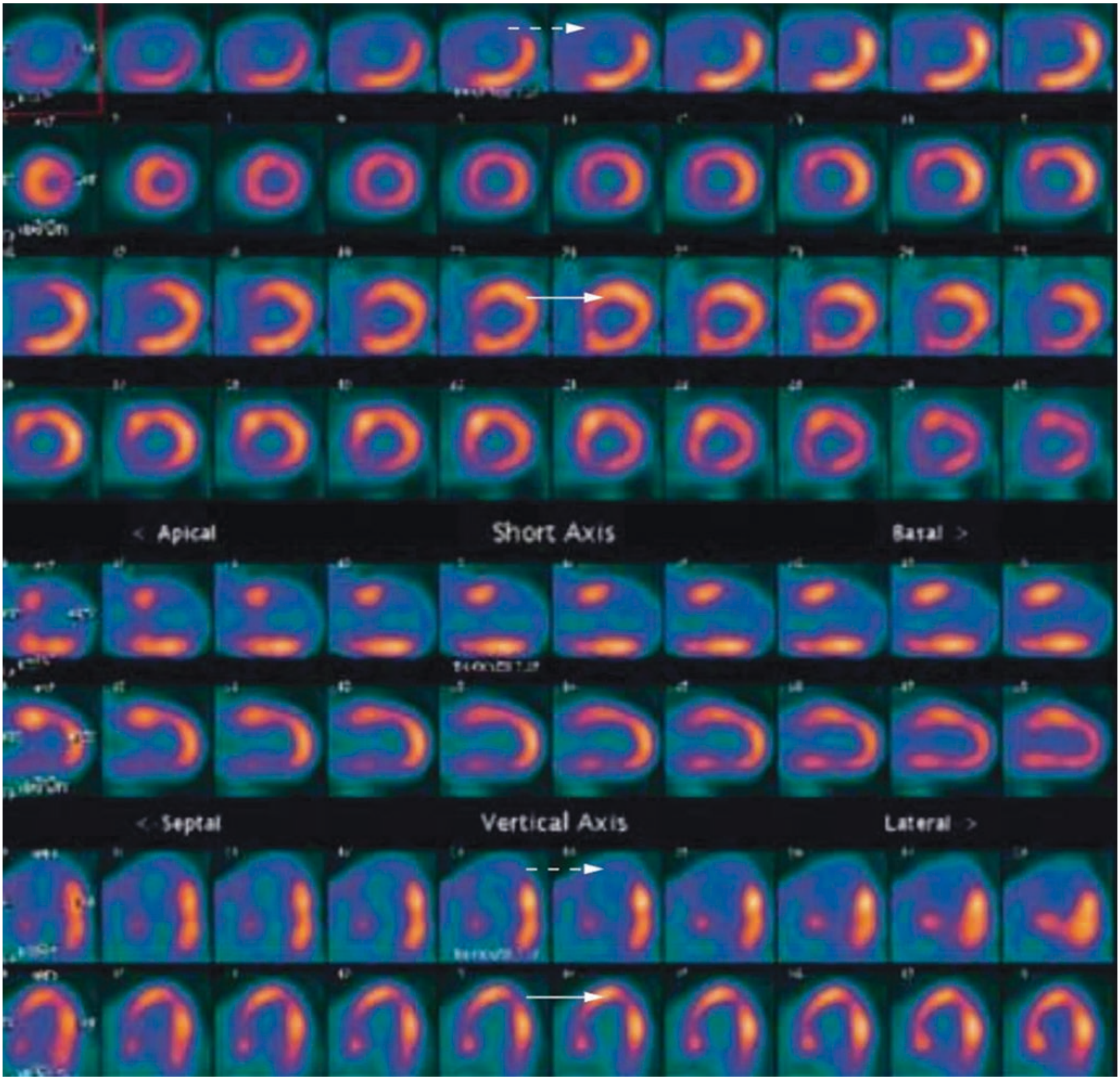
< Apical
Short Axis
Basal >
< Septal
Vertical Axis
Lateral >

Fig. 5.3 Perfusion defect on ^{82}Rb PET imaging (dashed arrow) shows normal uptake of ^{18}F-FDG demonstrating viable myocardium (solid arrow)

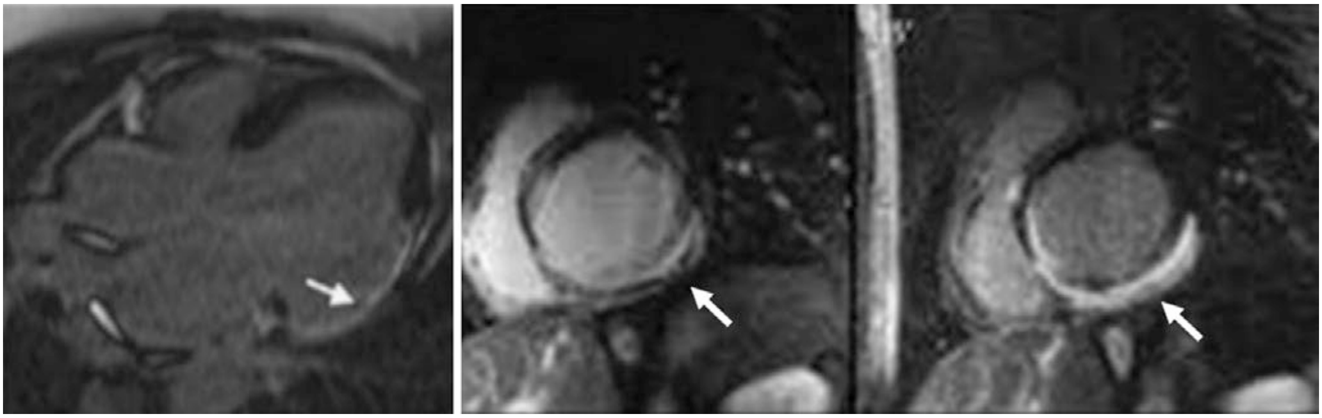

Fig. 5.4 Late gadolinium enhancement (arrow) demonstrates transmural infarct (non-viable myocardium) of the inferolateral and septal segments

end-diastolic segmental thickness, LGE and contractile reserve with dobutamine if necessary would yield a high sensitivity and specificity for determination of viability status [1, 3, 6, 13].

Of note, CMR contraindications such as claustrophobia and implanted devices preclude utility of CMR.

Miscellaneous

Myocardial contrast echocardiography (microvascular integrity assessment), myocardial strain and strain rate imaging by speckle echocardiography and cardiac CT perfusion and late hyper-enhancement (scar) imaging are the modalities [14–16] that have also been shown in studies to estimate myocardial viability with reasonable diagnostic accuracy. However, their use is not in vogue in the mainstream at present due to lack of experience, familiarity and expertise with the technology and non-superiority as compared to the other widely available techniques.

Choice of Viability Test

Choice of test to assess viability depends on several factors including patient's preference, limitations or contraindications of a particular study in a given patient, and local expertise and availability.

The degree of left ventricular (LV) remodeling and dysfunction may play a role in deciding which test to perform. Patients with extreme degrees of LV dilatation and segmental wall thinning are perhaps better served by PET metabolic imaging and CMR delayed enhancement imaging in conjunction with dobutamine stress to evaluate contractile reserve if necessary. In patients with mild to moderate degree of LV dysfunction and remodeling, dobutamine stress Echo and SPECT imaging may suffice.

Clinical Implications of Viability Status in Ischemic Cardiomyopathy

The wealth of evidence suggests that ischemic cardiomyopathy subjects with viable myocardium have a better prognosis with medical therapy and coronary revascularization compared to those with large amounts of scar burden who are at a higher risk for heart failure and ventricular arrhythmias [17, 18]. Most of these studies were under-powered, non-randomized and uncontrolled with inclusion of patients with much heterogeneity in the degree of LV dilatation, systolic dysfunction (ejection fraction), ischemia, and scar burden. Many observational studies and meta-analyses have demonstrated that revascularization of dysfunctional, ischemic, viable myocardium results in improved left ventricular function leading to better clinical outcomes [5, 6]. However, these studies were predated prior to making significant advancements in medical therapy of coronary artery disease (CAD) and cardiomyopathy.

On the contrary, the findings of the STICH (Surgical Treatment of Ischemic Heart Failure) Viability sub-study trial showed no differences in mortality outcomes between the medical versus medical and revascularization therapy groups in severe ischemic cardiomyopathy (LVEF <30%) with no demonstrable interaction between the viability status, surgical revascularization and outcomes. Several limitations of SITCH Viability sub-study are noteworthy. It was non-randomized, non-blinded, underpowered and viability testing was limited to SPECT or dobutamine echocardiography with arbitrary use of the thresholds to define the presence of viable or nonviable myocardium. In addition, it is important to recognize that these results are applicable to only patients with a severe degree of LV dilatation and reduced EF (<30%). In the STICH long-term follow up study however, the surgical revascularization group showed improved 10-year mortality outcomes compared to medical therapy alone, even though immediate, post-op mortality rates were higher [6]. In addition, few other studies have also been found to be supportive of the deterministic nature of the myocardial viability status on clinical outcomes of revascularization in ischemic cardiomyopathy [19].

Over the years, due to the conflicting data as illustrated above, there has been an ongoing debate regarding viability testing and coronary revascularization in patients with ischemic left ventricular dysfunction.

Nevertheless, given the convincing therapeutic and prognostic implications of the myocardial viability status in ischemic cardiomyopathy patients, 2013 ACCF/AHA heart failure management guidelines granted class IIa recommendation for the myocardial viability testing prior to revascularization in ischemic cardiomyopathy [7].

Coronary Revascularization in Ischemic Cardiomyopathy

Currently, the approach of therapy in ischemic cardiomyopathy is guideline based and widely accepted in clinical practice. First and foremost, it is essential to ensure everyone receives optimal guideline directed medical therapy.

Surgical revascularization has been shown to improve the mortality outcomes in patients with CAD and LV dysfunction with viable myocardium [18]. No mortality benefit was observed with percutaneous intervention, partly due to exclusion of high-risk patients such as left main disease, utilization of the older generation stents, and sub-par medical therapy.

In general, hibernating myocardium of approximately 20% of LV mass may be needed to make a meaningful impact in LV function (at least >5% improvement in LV ejection fraction) after revascularization [20]. On the same token, when myocardial scar is >20% of LV myocardium or the number of scar segments >4, success of LV global functional recovery with revascularization is less likely [21]. LV function improvement following the revascularization therapy may take from 6 months to a year or even longer in severely dysfunctional cases [22].

Viable, dysfunctional myocardium can be a wide spectrum from early stages of hibernation with minimal LV remodeling to late, pre-fibrotic state with ultra-structural changes of the cytoskeleton, manifesting as severe LV remodeling and segmental wall thinning [1]. Several factors may determine the recovery of contractile function and LV remodeling. As the degree of ischemia, extent of viable myocardium, and segmental wall thickness and LV ejection fraction increase with less of adverse LV remodeling, the chances of successful contractile recovery following the coronary revascularization may be high. On the contrary, viable myocardial segments in an adversely remodeled LV with thinned walls and severely reduced ejection fraction in association with large degree of scar burden may have less chances for the contractile improvement after the revascularization [18].

In ischemic cardiomyopathy with advanced LV systolic dysfunction, it is essential to optimize medical therapy and take a multitude of factors; presence or absence of angina, degree of myocardial ischemia, extent of the viable and non-viable myocardium, LV adverse remodeling, LV ejection fraction, patient's comorbidities and procedural risk into consideration prior to coronary revascularization.

As per ACCF/AHA 2013 heart failure guidelines, if the myocardium is viable, it is a class IIA recommendation for coronary revascularization if LV ejection fraction >35% and class IIA recommendation for either medical therapy or revascularization when LV ejection fraction <35% [23]. Revascularization may be considered in patients with an LV ejection fraction <35% and viable myocardium, if patients remain symptomatic on optimal medical therapy with an acceptable procedural risk and optimal coronary anatomy for the surgical or percutaneous intervention. Time to recovery can be delayed in these patients and it is not uncommon to take over a year in those with poor baseline characteristics [22].

Conclusions

In ischemic cardiomyopathy with mild to moderate systolic dysfunction and viable myocardium, coronary revascularization is recommended in addition to optimal medical therapy. In advanced ischemic cardiomyopathy with an LV ejection fraction <35% if the myocardial segments of diseased coronary territories are viable, revascularization should be considered, especially when there is no substantial improvement on optimal medial therapy alone. Patient's procedural risk and comorbidities must be considered. In this group of patients, further research is needed to determine the viability status with confidence and predict those who could benefit from coronary revascularization with improved LV function and better outcomes.

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6

Blood Conservation Strategies in Cardiac Surgery

David Royston

High Yield Facts

- Major transfusion (≥4 units red cells) still occurs in about 20–25% of patients presenting for cardiac surgery.
- Patient blood management (PBM) is a holistic concept of a patient centred, evidence based and multidisciplinary approach to optimize the use of blood and blood related products and thus improve patient outcomes.
- PBM programs are considered to have three components or pillars.
- Pillar one of PBM is about optimization of red cell mass and erythropoiesis prior to surgery.
- Pillar two of PBM is about minimizing blood loss.
- Pillar three of PBM is about maximizing the ability of the patient to cope with haematological irregularities during recovery period by optimizing tolerance to anaemia.

Introduction

The clinical observation of AIDS in 1981 and the discovery that it was caused by a retrovirus that could be transmitted in blood spurred many clinicians to embrace blood conservation techniques in cardiac surgical practice that had been suggested in the early 1960s [1]. However the threat of disease transmission has receded to be replaced by multiple studies showing that transfusion of red cell and haemostatic components is associated with both acute and longer-term adverse outcomes [2]. There is also growing awareness of the true financial cost to the health care sector of blood transfusions [3]. Despite this more recent studies have shown major transfusion (≥4 units red cells) still occurs in about 20–25% of patients presenting for cardiac surgery [4]. This suggests that there is still a need for further improvements in blood management and transfusion practice.

Since the turn of the millennium cardiac surgical and anaesthesia societies have issued advice and guidelines related to the incidence of these adverse events and also guidance on reducing transfusion burden [5, 6]. The most recent of these from the European Societies [7, 8] have focused on the more holistic concept of a patient centred, evidence based and multidisciplinary approach to optimize the use of blood and blood related products and thus improve patient outcomes. This approach has been termed Patient Blood Management (PBM) [9, 10]. PBM goes beyond the concept of appropriate use of blood products, because it aims to prevent and significantly reduce transfusion burden by addressing modifiable risk factors that may result in transfusion long before a transfusion is considered. The utility of this approach was shown with the publication of results from the PBM program in Western Australia [11], which is considered the largest such program in the World to date. It included 605,046 patients admitted to Western Australia's four major adult tertiary-care hospitals, with results showing the use of blood products was reduced by 41% during the study period. There were significant patient outcome benefits including a 28% reduction in hospital mortality, a 15% reduction in average hospital length of stay, a 21% decrease in hospital-acquired infections and a 31% decrease in the incidence of heart attack or stroke. Reduction in infections is particularly relevant to cardiac surgical practice, as infection and particularly pneumonia will lead to an increase in time on a ventilator and thus a prolonged duration of intensive care unit stay. Overall the reductions achieved resulted in a considerable cost saving to the health system.

The initial aspect of developing patient blood management is to identify the risk factors in patients that may increase the probability of receiving a transfusion during the course of their hospital stay. These have been identified by

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Table 6.1 Factors associated with increased risk of bleeding and need for transfusion[a]

Female gender
Insulin dependent diabetes
Type of procedure (non-CABG, combined procedure, surgery through prior sternotomy)
Dual anti-platelet therapy or low molecular weight heparin <5 days preoperatively
Low haemoglobin/haematocrit i.e. anaemia
Platelet count
Body mass index <20 kg/m^2
Age > 70 years
Surgical priority (emergency or salvage)
Estimated glomerular filtration rate < 60 mL/min

CABG coronary artery bypass grafting

[a] From Refs. [5, 6, 12–16]

Table 6.2 Factors in pillar one of patient blood management

Preoperative
• Screen for anaemia[a]
• Identify underlying disorder(s) causing anaemia
• Manage underlying disorder(s)
• Refer for further evaluation if necessary
• Treat iron deficiency, anaemia of chronic disease, iron-restricted erythropoiesis
Intraoperative
• Time surgery with optimization of red cell mass and erythropoiesis
Postoperative
• Consider use of erythropoiesis stimulation

[a] World Health Organisation definition of anaemia: Anaemia is a haemoglobin of ≤ 13 g/dL in adult males and ≤ 12 g /dL in adult females. A haemoglobin of ≤ 8 g/dL is regarded as an absolute contraindication for elective surgery

logistic regression analysis of large databases. Table 6.1 shows the patient characteristics that have been associated with such an increased risk [5, 6, 12–16].

Patient Blood Management programs are considered to have three components or pillars [17–19]. This chapter will discuss these in turn with particular emphasis on cardiac surgical practice.

Pillar One: Optimization of Red Cell Mass and Erythropoiesis Prior to Surgery

The components of the first pillar of patient blood management are outlined in Table 6.2.

Anaemia is defined by the World Health Organization as a haemoglobin concentration <13.0 g/dL for men and <12.0 g/dL for non-pregnant women. In a recent survey of cardiac surgery units in the United Kingdom about 30% of patients had anaemia at the time of their preoperative assessment [20]. The vast majority of these patients had an iron-deficiency type of anaemia. Iron-deficiency anemia is usually caused by blood loss, which can be occult from the digestive tract or more visible such as with menorrhagia. The second major factor with iron deficiency is insufficient dietary intake, as in vegetarians or vegans, or poor absorption of iron from food as may occur in Crohn's disease. Diagnosis is generally confirmed by a reduction in haemoglobin, mean corpuscular volume, mean corpuscular haemoglobin and plasma ferritin together with an increase in transferrin and total iron binding capacity. A plasma ferritin of <30 μg/L is pathognomonic of iron deficiency but as ferritin is an acute phase protein a value of <100 μg/L is used as the standard cutoff in most European PBM programs [21]. Patients with a very low haemoglobin (<11 g/dL in males and <10 g/dL in females) and those with positive occult blood in their stool should be referred for an urgent (<2 weeks) gastroenterological opinion [22]. Treatment is aimed to restore haemoglobin levels and red cell indices to normal, and to replenish iron stores [21, 22]. If time allows treatment should be with oral ferrous sulphate 200 mg or ferrous fumarate 300 mg two to three times per day. This dose should increase the haemoglobin by 2 g/dl over 3–4 weeks. If restoration of haemoglobin is more pressing then parenteral iron can be administered. Current preparations have a much-reduced incidence of allergic and other reactions and can be given over a short (10–30 min) period. The dose is calculated using the Ganzoni equation: Total Iron Deficiency (mg) = Weight (kg) × (Target haemoglobin − measured haemoglobin in g/dL) × 0.24 + 500 mg (estimated iron to replenish iron store in patient ≥35 kg in weight).

Pillar Two: Minimize Blood Loss

Factors in the second pillar of patient blood management are shown in Table 6.3.

Table 6.3 Factors in pillar two of patient blood management

Preoperative
• Identify family or history of bleeding risk
• Stop dual antiplatelet therapy. Safe to maintain on aspirin monotherapy
• Review antithrombotic therapy
Intraoperative
• Haemostasis oriented surgical technique
• Minimise haemodilution with small prime circuits and retrograde autologous priming
• Red cell salvage during surgery and from cardiopulmonary bypass circuit during chest closure
• Maintain temperature
• Prevent acidosis
• Drugs associated with improving haemostasis
Postoperative
• Vigilant monitoring of postoperative bleeding with early return to theatre for re-exploration if warranted
• Keep patient warm and prevent acidosis
• Minimise phlebotomy and iatrogenic blood loss
• Point of care diagnosis of coagulopathy and haemostasis/coagulation management.

Preoperative

Preoperative assessment should reveal any family or personal history of bleeding associated with trauma or surgery. Regarding patient characteristics, a number of studies have used regression analysis to determine the chance of having significant bleeding after cardiac surgery. One study from the UK [23] showed certain patient characteristics were associated with a clinical concern for bleeding. Somewhat surprisingly this predictability was not significantly improved by adding routine laboratory tests of coagulation or a battery of 28 point-of-care end points for coagulation and platelet function to the analysis [23]. However other studies have suggested that addition of data from viscoelastic tests performed during surgery to patient data will improve predictability of transfusion [24].

There is still debate about the balance between bleeding and thrombosis in patients with stents having non-cardiac surgery. However the bleeding risk for patients having cardiac surgery and especially with a period of cardiopulmonary bypass is clear. Guidelines [25] suggest that surgery should be postponed for 3 days if the patient is taking ticagrelor, 5 days with clopidogrel and 7 days for prasugrel. Alternately the degree of platelet inhibition can be assessed using platelet function analysis to guide the timing of surgery. This approach was associated with halving the time to surgery in clopidogrel treated patients [26].

Intraoperative

Surgical technique should be oriented to haemostasis and timely control of bleeding points. Anaesthetic technique should focus on maintaining cardiovascular stability and preventing hypertension.

The main mechanical foundation of managing red cell mass is to prevent haemodilution and the reinfusion of processed shed or sequestered blood.

Haemodilution prevention is achieved with low prime volumes or by using techniques such as retrograde autologous priming [27, 28]. Cell salvage techniques have been shown to be excellent for red cell conservation in a variety of surgeries [29] and have a special place in processing the contents of the cardiopulmonary bypass circuit after protamine administration and during chest closure.

Haemostasis is optimal if skin temperature is maintained and acidosis prevented.

There is considerable debate about pharmacological interventions to reduce bleeding. The vast majority of data showing a benefit to reduce transfusion burden [30] is related to the serine protease inhibitor aprotinin and the lysine analogue antifibrinolytics of which tranexamic acid is the most popular choice in Europe. These compounds are given a class 1 level of evidence A classification for effectiveness in the recent European guidelines [7, 8]. The main questions remaining are to establish if there is clear evidence for the efficacy superiority of one agent over the other and to establish if there are any safety concerns.

In their meta-analysis in the most recent Cochrane review [30] 3983 patients were included in studies directly comparing aprotinin with tranexamic acid. There was a 13% reduction in patients exposed to red cell transfusions ($p = 0.032$) in aprotinin treated patients. More recently, studies have compared data from the period prior to the voluntary withdrawal of aprotinin in 2007 with the subsequent period when aprotinin was not available and was thus substituted with tranexamic acid. For isolated first time coronary artery bypass surgery a French multicentre study [31] showed aprotinin was superior to tranexamic acid at reducing blood loss and transfusion especially in patients taking platelet active medication confirming the results of a randomized study in patients taking dual antiplatelet therapy [32] which showed a 60% reduction in transfusion of red cells and platelets in aprotinin treated patients. Perioperative blood transfusion in the French study [31] was also significantly lower in the aprotinin treated patients. This study also confirmed prior data that the plasma creatinine in aprotinin treated patients showed a statistically significant, but transient rise compared to those given tranexamic acid.

A single centre analysis from Bristol in the UK [33] analysed data from all the cardiac surgery performed at that unit. They used propensity analysis to match 1754 patients given aprotinin prior to licenses cessation with the same number treated with 4 grams of tranexamic acid after license cessation. Table 6.4 shows the data for transfusions in these two groups. In a subset of 501 of each of these groups identified at high risk of transfusion there was an increased risk of mortality following aprotinin suspension (Hazard Ratio 2.51; 95% Confidence Interval 1.00–6.29). This confirms similar findings from the group in Toronto Canada [34].

A higher risk of bleeding and need for transfusion is surgery to replace the ascending aorta using a period of hypothermic circulatory arrest. A study from Atlanta in the United States [35] with a single surgeon using the same technique of surgery and cardiopulmonary bypass showed a significant ($p < 0.01$) increase in transfusions of red cells, platelets, frozen plasma, cryoprecipitate and use of recombinant factor VIIa when tranexamic acid (≈4 g) was used instead of aprotinin.

Although aprotinin is superior to tranexamic acid in relation to bleeding and transfusion there are concerns over the safety of the therapy especially in the higher risk patient. Aprotinin competes with creatinine in the proximal convoluted tubule for the reuptake pathways and this leads to the transient rise in creatinine observed when aprotinin is used. As this mechanism also explains the creatinine changes with aminoglycosides and certain contrast agents it is not surprising that co-administration amplifies the creatinine rise.

Table 6.4 Data from Bristol Heart Centre (United Kingdom) reporting on transfusions following heart surgery at that institute

	All patients				
	Pre-cessation (n = 1754)		Post-cessation (n = 1754)		
Transfusion requirements	n	%	n	%	Odds ratio (CI)
RBC	706	40.3%	800	45.6%	1.24 (1.04–1.49)*
RBC ≥4 units	156	8.9%	248	14.1%	1.68 (1.29–2.21)**
Platelets	225	12.8%	423	24.1%	2.16 (1.69–2.76)**
FFP	140	8.0%	238	13.6%	1.81 (1.33–2.45)**
Cryoprecipitate	7	0.4%	27	1.5%	3.90 (1.32–11.51)*

[a] Data are from 1754 patients treated with aprotinin prior to licence cessation in 2007 and 1754 patient treated with4 gram tranexamic acid post license cessation. Data show numbers and proportions for red blood cell (RBC), platelets, fresh frozen plasma (FFP) and cryoprecipitate. Also shown are odds ratios (with 95% confidence intervals) for increased transfusion in post cessation patients. *p < 0.05, **p < 0.01. Data are from Walkden et al. [33]

The final problem regarding creatinine is that renal function deteriorates with advancing age and patients over 70–75 years of age have a higher risk of bleeding and transfusion. There are virtually no safety data in this group of patients so the regulators have asked for the market authorisation holder (Nordic Pharma. BV) to collect data for patient usage and adverse outcomes. Participation in the Nordic Aprotinin Patient Registry (NAPaR) is a condition for sale of aprotinin in Europe [36]. Hypersensitivity reaction on a second exposure within 12 months is a recognized problem with the use of aprotinin although the mechanism is unclear.

With regard to safety of tranexamic acid, the major risk that has emerged over the past few years is increased seizure activity. The potential mechanism for altering the excitatory neuronal state is that the lysine analogues have marked structural homology with gamma amino butyric acid (GABA) and act as competitive inhibitors in the central nervous system [37, 38]. A meta-analysis of 45,235 patients showed the risk was increased by about four fold [39]. More worrying is the data from the ATACAS study [15], which was a multinational, randomized controlled trial in 4631 patients. The relative risk of having a seizure in this study when receiving tranexamic acid was 7.6 fold and this was not affected by halving the dose of tranexamic acid. More worrying aspect from this study was that the authors estimated that those patients who had a seizure were 22 times more likely to have a permanent stroke and 9.5 time more likely to die. If this data is universally applied to the yearly cardiac surgery numbers for the UK than 250 patients would have perioperative seizures causally associated with the use of tranexamic acid. Of these if the ATACAS figures were repeated about 25 would die and about 100 would have a permanent stroke.

Postoperative

Monitoring the rate of bleeding is a fundamental of patient management. There should be an algorithm in place to determine interventions and a low threshold for returning the patient to theatre for re-exploration.

Phlebotomy has been identified as one of the main factors in blood losses in the intensive care unit [40]. This is especially the case in more long-term patients who were not actively bleeding. For example, a 3.5 mL increase in daily phlebotomy volume was reported to double the odds of being transfused by day 21 post surgery [41]. Using closed loop-sampling systems and microsample point-of-care tests (as in paediatric practice) should be actively considered as part of the patient blood management program. Postoperative coagulopathy management is improved if a viscoelastic point-of-care algorithm is utilized. A Cochrane review [42] has analysed articles using either thrombelastography (TEG®) or thromboelastometry (RoTEM®) when compared with transfusion guided by any method. These analyses demonstrated a statistically significant effect of TEG® or RoTEM® compared to any comparison on the proportion of participants transfused with pooled red blood cells (PRBCs) (RR 0.86, 95% CI 0.79–0.94:10 studies, 832 participants, fresh frozen plasma (FFP) (RR 0.57, 95% CI 0.33–0.96; 8 studies, 761 participants, platelets (RR 0.73, 95% CI 0.60–0.88; 10 studies, 832 participants, and overall haemostatic transfusion with FFP or platelets. However, the authors commented on the low quality of the evidence and suggested further evaluation of the technologies is required. Interestingly use of point-of-care platelet function analysis has failed to show benefits in the postoperative, as opposed to preoperative, period to reduce transfusion volumes.

As with intraoperative management maintaining skin temperature and preventing acidosis are very important.

Pillar Three: Maximize the Ability of the Patient to Cope with Haematological Irregularities During Recovery Period by Optimizing Tolerance to Anaemia

Factors in this pillar of patient blood management are shown in Table 6.5.

At the preoperative assessment the patient should be informed as to the likely strategy regarding bleeding and transfusions relevant to the planned cardiac surgery procedure.

Table 6.5 Factors in pillar three of patient blood management

Preoperative
• Make discussions with patient inclusive in management plan
• Assess/Optimize cardiopulmonary function and physiological reserves
• Develop patient specific management plan to minimize blood loss, optimize haemoglobin and manage anaemia
Intraoperative
• Optimize cardiac output, ventilation and oxygenation
• Apply restrictive red cell transfusion strategies
Postoperative
• Treat anaemia
• Maximize oxygen delivery
• Minimize oxygen consumption
• Avoid or treat infection promptly
• Continue restrictive transfusion strategy

Many hospitals have patient literature explaining this or have their patient blood management plan available.

It seems intuitive to optimise cardiorespiratory function in the preoperative period (prehabilitation) in the belief that this will provide a reserve in the perioperative and early postoperative period to allow the oxygen delivery to be maximized without requiring a red cell transfusion. Patients with incipient cardiac failure should be receiving appropriate therapy with diuretics, angiotensin converting enzyme inhibitors or receptor blockers and beta-adrenergic blockade. Postoperative pulmonary complications increase the use of medical resources, length of hospital stay and healthcare costs. A six-factor model (age ≥ 70 years, productive cough, smoking, diabetes mellitus, inspiratory vital capacity and maximum expiratory mouth pressure lower than 75% of the predicted value) has been used to predict the risk of developing pulmonary complications in patients undergoing elective cardiac surgery [43].

In the higher risk patient physiotherapy aimed at improving inspiratory muscle function has been shown to have significant benefits [44].

There is increasing literature to show that a restrictive transfusion strategy (threshold 7.0–8.0 g/dL) is not inferior to a more liberal strategy (threshold 9.0–10.0 g/dL) when mortality and morbidities are compared [45–47]. However one UK study (TITRe2) suggested mortality might be increased with a restrictive policy. The study has however been criticised concerning certain confounders and the transfusion thresholds [7, 8]. One further concern about the use of restrictive policies is that the patient may not mobilise as rapidly as a patient with a higher haemoglobin, and thus oxygen delivery. The group in Milan has addressed this as all patients in Italy are provided with rehabilitation after their surgery at a specialist unit. The test of activity used was the 6-min walking distance. This was significantly lower in patients on admission to the rehabilitation hospital if the haemoglobin was less than 10 g/dL. However it was not outside the expected range and improved with a period of rehabilitation to be the same as other patients [48].

Conclusion

Patient blood management is an evidence-based, multidisciplinary, multimodal, and patient-tailored approach aimed at reducing or eliminating the need for allogeneic transfusion by managing anaemia, perioperative blood conservation, surgical haemostasis, and blood as well as plasma-derived products use. For most patients it is possible to minimise or avoid blood transfusion by a ‘standard of care’ management of a patient’s own blood by optimising and preserving haematopoietic reserves in conjunction with tolerating the effects of deficiencies.

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Inotropes, Vasopressors and Vasodilators

7

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High Yield Facts

- Postoperative pharmacological therapy with inotropes and vasopressors is frequently required to treat confirmed myocardial dysfunction or clinically relevant hypotension and vasoplegia.
- Myocardial dysfunction, clinically relevant hypotension and vasoplegia are of major concern, as these conditions are prevalent, and are associated with greater morbidity and mortality.
- The "ideal" inotrope remains elusive and all inotropic agents also affect the vasculature: i.e., inopressors or inodilators.
- While inotropy can be improved by various agents, they usually increase myocardial oxygen consumption and might be proarrhythmogenic (exception levosimendan).
- Beyond contractility, there should be a clinical "obsession" with coronary and distal organ perfusion pressure during inotropic support.
- Due to side effects, inotropes are most often indicated for defined clinical situations with confirmed ventricular dysfunction and/or failing vasculature and should be used at the lowest dose required with optimal haemodynamic monitoring and frequent reassessment of the circulation if more than 2 inotropes/vasopressors have been initiated.
- Combination of drugs at lower doses may be advantageous over a single agent used at high dose due to increased adverse side-effects.
- Inotropes can be classified as potent and milder catecholamines (adrenaline, isoproterenol, noradrenaline vs. dobutamine, dopamine and dopexamine) for severe versus moderate myocardial dysfunction for clinical purposes.
- Early use of vasopressin at low to moderate doses may have catecholamine sparing effects, reducing side effects in conditions of catecholamine resistance, such as sepsis, severe SIRS, vasoplegia or beta blockade.
- Recent clinical trials with levosimendan demonstrated physiological improvements in low cardiac output syndrome but no major outcome benefits. Current indication for its use is coronary artery disease with severe left ventricular impairment.

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The Case for Inotropic Support in Cardiac Surgery

The circulatory determination of normal human life at rest depends on a remarkable and wonderfully intricate integration of multiple physiological processes linking cardiac pump function through electromechanical myocardial coupling to appropriate stroke volume of normally composed blood by each heart beat at a tightly regulated frequency, distributing this output serially through the pulmonary and systemic circulation via the dynamically regulated vasculature on the basis of resting vascular tone and pulmonary and systemic resistances. This resting state is capable of responding promptly and dynamically to a myriad of endogenous and environmental factors based on neurohormonal changes matching cardiac output to global and regional demands and balancing oxygen delivery for consumption at individual organ level.

Classical cardiac surgery conducted with traditional cardioplegia and cardiopulmonary bypass (CPB) commonly alters this normal physiology in multiple ways including patient related preoperative factors, surgery induced changes in electric and contractile properties of the right and left ventricles, alterations in circulating blood volume, composition and physicochemical properties of blood and microvascular alterations involving abnormal vascular tone and increased permeability [1].

Depending on their physiological reserve, the majority of patients recover from these transient changes and experience a largely uneventful postoperative course. However, an increasingly significant number of patients deviate from such recovery and fail to strive after the operation and commonly, the changes together with reduced physiological reserves result in low cardiac output state, inappropriate distribution of cardiac output with inefficient oxygen delivery at the expense of pulmonary and systemic complications, increased postoperative morbidity and single or multiple organ failure [2, 3].

What Are We Treating and What Are the Practical Dilemmas?

Our medical training advocates the homeostasis concept to attempt to maintain the physiological integration in a near normal range. Thus, inotropic support, broader pharmacological therapy to support the circulation and ultimately mechanical support are at the disposal of (cardiac) anaesthesia and surgical teams to optimally manage our patients with perioperative hemodynamic instability at different critical stages of surgery such as induction of anaesthesia, separation from CPB and chest closure.

The principal indication for inotropic support is anticipated or manifest hemodynamic instability ranging from low cardiac output to established shock stages [2, 3]. The interrelationship of cardiac output, perfusion pressure and vascular resistance, however, dictates that a thorough mechanistic and exact evaluation is required to determine which component is primarily responsible for the instability. This may not be straightforward, and more than one component could be affected. For instance, both myocardial dysfunction and low systemic vascular resistance (SVR) could be contributing to low mean arterial pressure (MAP) in septic or systemic inflammatory conditions. A systematic evaluation of right ventricular function, pulmonary hypertension, left ventricular diastolic and systolic function and assessment of systemic vascular resistances are all necessary to obtain a complete picture of pulmonary and systemic hemodynamics. This normally requires different monitoring modalities including pressure, flow measurements and imaging usually using echocardiography, integrating the individual data into a coherent assessment of circulation.

Some common clinical scenarios associated with haemodynamic instability and their treatment options are listed in Table 7.1.

Ventricular Dysfunction

Many cardiac patients by definition suffer from a chronic cardiovascular condition (commonly systemic atherosclerosis and coronary artery disease) associated with comorbidities, such as diabetic cardiomyopathy and/or cardiac adaptation to essential or secondary hypertension with or without valvular disease. While most patients present with preserved biventricular function, left ventricular (LV) and/or right ventricular (RV) systolic dysfunction are not uncommon and many patients suffer from variable degrees of LV diastolic dysfunction or both systolic and diastolic dysfunction.

Predictably, routine cardiac surgery performed with aortic cross clamping produces a degree of myocardial ischemia with a decline in ventricular function despite cardioplegic preservation and eventual reperfusion in the first few hours after cardiac surgery [4, 5]. This may be accentuated by the negative inotropic effects of some of the anaesthetic agents, although nowadays, the practiced balanced cardiac anaesthesia is fairly cardiac neutral.

Circulatory Volume Status and Ventricular Preload

The surgery and anaesthetic management may cause major fluid shifts necessitating transfusion of crystalloids, colloids, and/or blood products in order to prevent hypovolemia and severe haemodilution. These may have an impact on cardiac

Table 7.1 Treatment strategies and inotropes used during optimisation of various commonly occurring clinical situations

RV function	LV function	MAP	Cardiac index	Causes	Treatment strategies	Inotropic agents
nl	nl	nl	nl	Normal daily life General anesthesia	None	None
nl	nl	nl/low	nl/low	Induction anesthesia Hypovolemia	Fluids Inopressors	Phenylephrine Norepinephrine Metaraminol Ephedrine
nl	↓	nl/low	nl/low	LV failure due to: Hypovolemia Infarction Mitral valve and/or Aortic valve pathology	Fluids IABP Inodilators Inopressors	Dobutamine Milrinone Norepinephrine Epinephrine
↓	nl	nl/low	low	RV failure due to: Hypovolemia Arterial pulmonary hypertension RV pressure and/or volume overload	Fluids NO Pulmonary vasodilators Inopressors	Iloprost, Milrinone Bosentan Sildenafil Epinephrine Norepinephrine
↓	↓	low	low	RV and LV failure DCMP ICMP	NO Pulmonary vasodilators Inopressors Inodilators	Iloprost, Milrinone Bosentan Sildenafil Epinephrine Norepinephrine

↓ decreased, *IABP* intra-arotic balloon pump, *LV* left ventricular, *MAP* mean arterial pressure, *nl* normal, *NO* nitric oxide, *RV* right ventricular

performance by altered preload via the Frank-Starling mechanism and low stroke volume in hypovolaemic states, or RV and/or LV volume overload at excessive fluid balance with the consequence of reduced oxygen delivery to the heart and peripheral tissues.

Vascular Resistances and Vasoplegia

Endogenous basal vascular tone (determined by the balance of endothelial vasodilator and vasoconstrictor mechanisms), the activity of autonomic nervous system through parasympathetic and sympathetic influences and local and circulating vasoactive mediators determine regional and total systemic vascular resistances. While there are a few situations where surgery is associated with increased vasoconstriction and higher than normal vascular resistances, routine cardiac surgery commonly produces a low systemic vascular resistance state ranging from a mild vasodilator state to severe vasoplegia. Among the multiple mechanisms, a systemic inflammatory response syndrome (SIRS) and the side-effects of anaesthetic agents may play a major role.

SIRS representing a whole-body inflammatory reaction is believed to be due at least in part by blood contact with foreign surfaces (e.g., extracorporeal circuit) and resultant activation of blood leukocytes and plasma cascades of coagulation and complement [6–8]. The magnitude of SIRS varies among cardiac patients, but the persistence of severe inflammation is considered harmful and appears to significantly influence postoperative patient journey. Activation of a large number of potentially important mediators has been identified and among these, pro-inflammatory cytokines have been proposed to be responsible for many deleterious effects of CPB.

Induction and maintenance of anaesthesia and analgesia causes reduction in sympathetic tone which may result in a vasodilated state. Furthermore, specific anaesthetic agents including propofol exhibit direct vasodilatory properties. Some muscle relaxants are notorious for histamine release that may also contribute to vasodilation.

Finally, cardiac surgery may reduce splanchnic perfusion with the potential of causing splanchnic hypoxemia, bacterial translocation of the normal intestinal flora to the bloodstream and the release of bacterial products which may cause endotoxaemia and a sepsis like syndrome. Similar mechanisms are responsible for a shock state or low SVR state in patients with ongoing infections.

Unless there is a compensatory increase in cardiac output, low SVR will manifest as a degree of hypotension. This reduces perfusion pressure to the myocardium and peripheral organs and if remains untreated, produces a vicious circle with more severe hypotension and multiple organ dysfunction. Therefore, maintenance of adequate perfusion pressure should be a priority with a degree of "obsession" in the overall management of the cardiac surgical patient.

While haemodynamic instability is an urgent situation, the modern conduct of cardiac surgery normally allows exact evaluation of the overall situation with the pressure, flow monitoring, imaging and direct visualisation of heart enabling identification of principle problems and timely corrections. However, 2 situations should be considered as a major haemodynamic emergency requiring prompt assessment and action:

- *Hypotension with ongoing myocardial ischaemia*: Myocardial performance critically depends on adequate coronary blood flow. In the setting of severe coronary artery disease (CAD) distal blood flow across the narrowed coronary artery or to the subendocardium of a hypertrophied ventricle (such in aortic stenosis) cannot be guaranteed with certainty but will critically depend on proximal perfusion pressures. Thus, correction of hypotension by pressor agents is a priority to prevent further deterioration of myocardial ischemia and prevention of hypotension is normally easier than recovering from myocardial ischemia related ventricular dysfunction.
- *Systemic hypotension in the presence of high central venous pressure (CVP)*: This usually signals RV failure. This situation can deteriorate very rapidly and immediate RV offloading (reverse Trendelenburg position, administration of nitrates, diuresis) , reduction of pulmonary vascular resistance (hyperoxia, inhaled vasodilators) and administration of contractile agents (calcium, adrenaline) is required.

Principles of Vasoactive Support

1. Prior to considering inotropic support to treat hypotension, non-pharmacological strategies should be optimised. Among these the most important is volume therapy. One major lesson from goal directed therapies is that while inotropic therapies are important components, most goal directed therapy interventions increase volume status significantly compared to routine management [9]. Thus, one could reasonably assume a degree of relative hypovolaemia in most situations of hemodynamic instability and it is reasonable to start troubleshooting by correcting hypovolaemia. Caution is required with the history of LV and RV dysfunction. Volume status is not always easy to assess as there is notoriously weak relationship between CVP and ventricular preload in cardiac surgical populations. However, direct assessment of LV and RV loading by echocardiography is nowadays a routine intraoperative tool.
2. Similarly, acid-base status should be corrected as most intracellular signalling and second messenger systems work optimally at normal pH and acid base status.
3. With a focus on hypotension and as prelude to any inotropic interventions three principle questions should be answered:
    (a) Is there a significant LV or RV dysfunction with reduced contractility?
    (b) Is there systemic vasodilation/SIRS status?
    (c) Is there elevated pulmonary vascular resistance (PVR)?
4. Answers to these questions require knowledge of patient history and the actual clinical context especially recognition of recent surgical and anaesthesia interventions (presence of pre-existing ventricular compromise, long cardiopulmonary bypass, blood loss, any infection component).
5. All pressure measurement should be integrated into some of the broader preload and afterload concepts.
6. Echocardiography is extremely valuable to confirm contractile dysfunction, global ventricular hypokinesis, severe regional wall motion abnormalities and valvular problems. Assessment of mitral and tricuspid regurgitation may direct attention to pulmonary hypertension with estimates of systolic pulmonary artery pressures and RV afterload.
7. The authors advocate the use of exact haemodynamic evaluation in severe haemodynamic instability and monitoring continuous cardiac output with attention to the derived variables namely SVR and PVR and their indices. Continuous monitoring of SvO_2 provides an additional global monitoring tool and very prompt assessment of the influence of haemodynamic interventions.
8. Inotropic management should recognise that all individual inotropes exhibit a spectrum of different haemodynamic effects that largely depend on the dose of the agent.
9. Apart from the direct actions on the heart, the most important effects are on the vasculature and the effect of each inotropic agents on SVR should always be considered. This phenomenon encompasses a wide spectrum of vascular effects from strong vasodilation to strong vasoconstriction. This is well represented by our analysis of published data on direct effects of various inotropic agents on SVR and the trend established from these data (Fig. 7.1).
10. Effective synergy can be achieved by combination of several agents based on basic knowledge of their molecular and cellular mode of actions: for instance, combining adenylate cyclase activating inotropes with phosphodiesterase inhibitors based on synergistic effects on steady state cyclic nucleotide levels or with agents of different mechanisms of action such as calcium sensitizers.
11. All these agents have their unique adverse effect profile usually causing tachyarrhythmias, cardiotoxicity, pro-inflammatory and pro-apoptotic effects, and an increase in intracellular calcium concentration which may lead to increased myocardial and vascular oxygen consumption. Such side effects cannot be ignored as they modify the acute haemodynamic response but may also influence longer term outcomes. There is ongoing controversy whether the use of inotropes in cardiothoracic

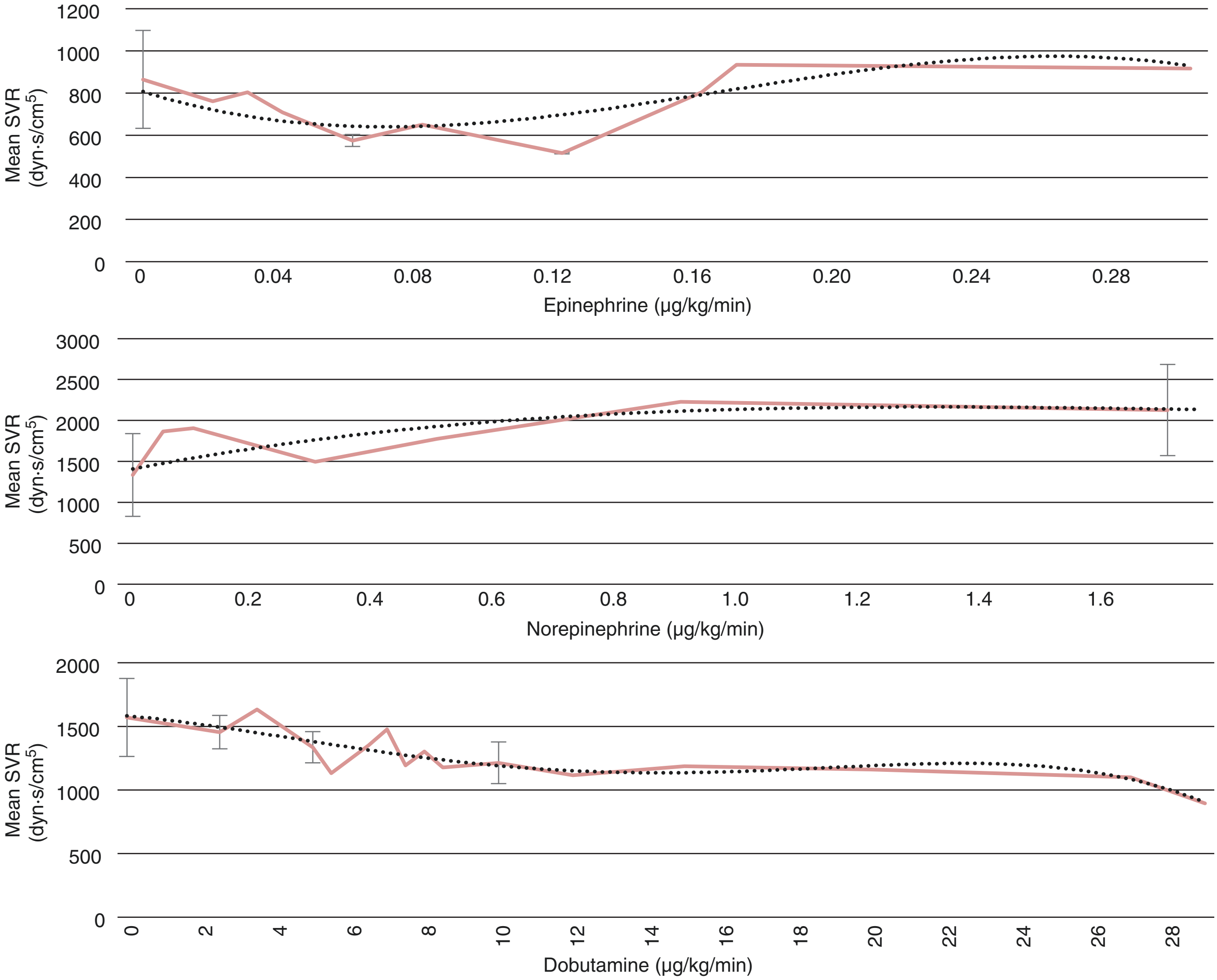

Fig. 7.1 Examples of dose-dependent effects on systemic vascular resistance (SVR) of common inotropic agents (epinephrine, norepinephrine and dobutamine) based on literature review of inotropic dose responses. Trendline shown in black

surgery is associated with an increase in mortality. Indeed, observational studies have suggested that inotrope use may increase mortality, although these findings have not been confirmed in randomized clinical trials [10].

12. Much of our pharmacological and physiological data in this field have been derived from healthy animal and isolated model experiments. These classical concepts may only partially apply to complex clinical situations. For instance, healthy aging may have dramatic influence on the biochemical and physiological responses by a given stimulator. Equally important, comorbidities such as essential hypertension, diabetes, and chronic inflammation dramatically changes the hormonal environment, the levels of circulating cathecholamines and the intrinsic myocardial and vascular substrates of inotropy and vascular tone. Moreover, concomitant pharmacological therapy dramatically shifts this delicate balance. For instance, the widespread use of beta blockers in the cardiac surgery population renders most of our inotropes less efficient as many of them utilise the same biochemical pathway to influence the heart. The adrenergic theory thus dictates that the action of our mixed inotropes is shifted to become vasopressors in the presence of beta blockade. Similarly, the preoperative use of angiotensin converting enzyme (ACE) inhibitors promotes vasodilation through interference with the angiotensin system and reduced breakdown of bradykinin affecting many components of vascular regulation. Thus, new perioperative inotropic and vasoactive support should be put into context of these patient related factors and a good estimate of the actual status of endogenous vasoactive mediators and the effect of preoperative pharmacological therapy.

13. For all these reasons inotropes should only be used when strictly indicated, such as in patients at high risk for cardiac failure and organ hypoperfusion and should be titrated to achieve a beneficial hemodynamic response and to avoid or minimize adverse side effects [11]. Such efficacy and side effects have to be continuously monitored and evaluated. Weaning from inotropic support should be a clinical priority and it is vital for the perioperative management to assess if the following conditions still warrant ongoing treatment:
    (a) Is there need to correct hypotension to provide adequate organ perfusion?
    (b) Is support required for acute heart failure?
    (c) Is there evidence of failing peripheral vasculature?

Clinical Classification of Haemodynamically Active Pharmacological Agents

The clinical classification is usually done by considering the principle dominant pharmacological action on myocardial contractility taking into consideration the direct vasoactive properties. There is a continuum and spectrum of the strength of inotropic action and a predominant vasodilatory or vasoconstrictor side effect. According to the prevailing mechanism of action, inotropes can be classified as

(a) Inoconstrictor (i.e., having positive inotropic and vasoconstrictive effects).
(b) Inodilators (i.e., having positive inotropic and vasodilating effects).

In the haemodynamic context, it is useful to contrast these inotropes to agents with more direct effects on vascular tone with much less pronounced effect on myocardial contractility such as

(c) Vasopressors (i.e., having predominantly vasoconstrictive effect).
(d) Vasodilators (i.e., having predominantly vasodilator effects).

Description and Clinical Utility of Inotropes and Vasoactive Agents

Three different categories of inotropes are currently available: sympathomimetic agents, phosphodiesterase-type III inhibitors and calcium sensitizers (levosimendan).

Sympathomimetic Drugs

Epinephrine (Adrenaline)

The principle effects on the myocardium are positive inotropic and chronotropic action. Regarding the peripheral vasculature, it is a vasodilator at low dose but vasoconstrictor at high dose and also depending on vascular beds. At low dose, the net clinical effects are increased cardiac output, and mild reduction in SVR; increase in effective circulating volume and increased venous return with rising systolic blood pressure (BP) and reduction in diastolic BP at lower doses. At higher doses a rise in SVR predominates with consequent decrease in cardiac output and rise in both systolic and diastolic BP. Metabolically, it has anti-insulin actions and may cause hyperglycemia and lactic acidosis.

Principal use is supporting right and left ventricular function in heart transplantation, right ventricular function during left ventricular assist device (LVAD) implantation and in general inotropic support in acute heart failure, cardiogenic shock and cardiopulmonary resuscitation [12–14]. Indeed, in patients with cardiogenic shock, epinephrine has been shown to effectively improve global hemodynamics, while decreasing intestinal perfusion [12].

Among major side effects are increased incidence of dysrhythmias due to irritability of autonomic conducting system. It may also precipitate spasm of coronary arteries and angina in patients with CAD and ischemic heart disease (IHD). It may worsen LV outflow tract obstruction in hypertrophic cardiomyopathy or in conditions of systolic anterior motion of the mitral valve or LV hypertrophy.

Norepinephrine (Noradrenaline)

Compared to epinephrine, norepinephrine exhibits a weaker inotropic effect but is a powerful inoconstrictor. This characteristic enabled norepinephrine to become a standard vasopressor in cardiothoracic surgery to treat mild hypotension and to counteract the SIRS response. It is also the first line of treatment in refractory hypotension [15, 16]. Administration of norepinephrine may result in a slight decrease in cardiac output and oxygen delivery due to increased afterload. The effect on organ perfusion varies and is determined by the net effect of increasing perfusion pressure and increased vascular resistance. It may be useful in cardiogenic shock due to increases in coronary perfusion pressure and improvement of myocardial performance [15, 16].

Dopamine

While being an inodilator at low doses, dopamine becomes an inoconstrictor at doses >5 μg/kg/min). It has been demonstrated to increase cardiac output in patients with septic shock. This effect appears to be due to increased stroke volume as it has minimal effect on SVR. While dopamine increases urine output in different settings, the promise of prevention of renal failure in critically ill patients has not realised. To the contrary, the use of dopamine as a first-line vasopressor increased mortality in patients with cardiogenic shock when compared to noradrenaline in a large international multicenter trial [13]. This recognition has led to a dramatic reduction in the use of dopamine in patients with perioperative cardiac failure.

Dobutamine

Dobutamine is a synthetic catecholamine possessing the same basic structure of dopamine with a bulky ring substitution on the terminal amino group. Due to its attractive combination of haemodynamic properties including strong positive inotropy with mild chronotropy and overall peripheral effect of an increase in blood flow to skeletal muscle and splanchnic circulation, dobutamine has become the standard inotrope in perioperative medicine. While it is believed to be a pulmonary vasodilator, the decrease in PVR generally results from increases in cardiac output due to an enhanced contractility [17]. High doses can cause severe tachycardia and might even result in pulmonary vasoconstriction, depending upon the baseline tone.

Phosphodiesterase-Type III Inhibitors

Selective phosphodiesterase-type III inhibitors (enoximone, milrinone) increase intracellular levels of the second messenger cyclic adenosine monophosphate. The degree of this response depends on the expression and activity of this enzyme in the myocardium and vasculature and on the stimulation level of the adenylate cyclase by endogenous and exogenous agonists. In particular these drugs cause a positive inotropic effect in the heart, and also vasodilation with net results of increased cardiac contractility and output and decreased preload and afterload with mild/moderate chronotropic effect [18].

These characteristics make them useful for the short-term treatment for acute on chronic severe cardiac failure, for instance, in decompensated patients bridged to transplant or LVADs. Intraoperatively, low dose infusion may help with moderate ventricular dysfunction if SVR can be guaranteed. Caution must be exercised with co-administration of other inodilators due to their synergistic effect and especially regarding the augmented effects on vasodilation. Systemic hypotension is an ever-existing possibility, which frequently necessitates the administration of vasopressors. They are contraindicated in vasoplegic states and severe SIRS during and following CPB.

As they are metabolised in the liver and excreted by the kidney, liver and renal dysfunction will lead to accumulation of these agents in the circulation with potentially disastrous consequences. Therefore, SVR should also be tightly monitored and controlled and plasma levels of milrinone monitored if its prolonged use is warranted by the clinical scenario. Such vigilance with the use of this class of drugs cannot be overemphasized as it has been suggested that the use of milrinone in cardiac surgery was associated with an increase in mortality [18].

Levosimendan

The main mechanisms of action of levosimendan include increasing the sensitivity of cardiac troponin C to calcium as a “calcium-sensitizer” and opening of K^+-ATP channels in smooth muscle cells and mitochondria [19, 20]. This mechanism of action conveys positive inotropy plus vasodilation (“inodilator”) and cardioprotection with anti-stunning and anti-inflammatory effects. In contrast to other inotropes, levosimendan does not raise intracellular calcium-levels thus, myocardial oxygen consumption is not increased and therefore, it does not produce adverse events with tachyarrhythmias. Moreover, levosimendan improves microcirculation and renal function.

While recent large RCTs (LICORN, CHEETAH, and LEVO-CTS) demonstrated that levosimendan was safe and well tolerated in patients with low LV ejection fraction undergoing cardiac surgery with CPB, they failed to show improvement in major clinical outcomes for regulatory approval [21, 22]. However, subsequent consensus statements and meta-analyses still advocate physiological and clinical benefits in reducing low output syndrome following surgery, especially in the CABG population with severe ventricular dysfunction (LVEF <30%) [22].

Vasopressin

Arginine vasopressin (AVP) also known as antidiuretic hormone, is a peptide endogenously secreted by the posterior pituitary gland in response to appropriate stimuli that includes systemic hypoperfusion states. Vasopressin administration results in an intense peripheral vasoconstriction through direct action on vasopressin receptors on the vascular smooth muscle cells. A relative or absolute deficiency of endogenous vasopressin is associated with vasodilatory shock after CPB. Low doses of AVP and its synthetic analogue terlipressin can restore vasomotor tone in conditions that are resistant to catecholamines, with relative preservation of renal blood flow and urine output. They could also be useful in the treatment of refractory arterial hypotension in other conditions lowering the amount of catecholamines needed thereby allowing a more balanced vasopressor therapy [23, 24].

Special Focus on the Pulmonary Circulation

Due to the well-known sensitivity of the RV to increases in afterload, administration of pulmonary vasodilators remains one of the mainstays in the management of RV dysfunction [25]. There are two approaches. The intravenous application of "pulmonary" vasodilators (e.g., prostacyclins) is effective in reducing PVR but due to nonselectivity, they also result in systemic hypotension and may worsen RV function, ventilation/perfusion matching and increase pulmonary right-left shunting.

Administration of some vasodilators via inhalation/nebulization may confirm a degree of selective pulmonary vasodilation. Inhaled nitric oxide (iNO) and prostacyclins (PGI_2)] are metabolized within the lungs before reaching the systemic circulation and hence systemic arterial hypotension is prevented. Moreover, as the inhalation route only delivers vasodilators to ventilated lung areas, this approach improves ventilation-perfusion matching.

The Nitric Oxide (NO) Pathway

This pathway can be modulated by the direct administration of NO, inhibition of phosphodiesterase-type V (PDE-V) (the enzyme responsible for degradation of cyclic guanine monophosphate (cGMP) or stimulation of soluble guanylate cyclase (sGC).

Inhaled nitric oxide (iNO) is a powerful vasodilator through its action by increasing intracellular levels of the second messenger cGMP. iNO reduces elevated PVR in many situations with a consecutive improvement of RV performance and increases oxygenation in lung injury [26, 27]. iNO has been in clinical use for several decades [16] mainly for the management of perioperative pulmonary hypertension in numerous clinical settings, including heart transplantation, lung transplantation, placement of LVAD and in congenital cardiac surgery [26, 27]. Many institutions advocate prophylactic use of iNO in cardiac surgery prior to major surgical insult. However, there is ongoing debate and lack of correctly powered definite clinical trials regarding influence of iNO on hard outcomes in high risk cardiac surgery. Efficacy is based on small scale trials and European consensus recommendations rather than high quality evidence. For instance, in a blinded randomized controlled trial in LVAD implantation, iNO reduced RV dysfunction and the requirement of right ventricular assist device (RVAD) implantation by nearly 50%, however these results did not achieve statistical significance [28]. Further large-scale trials and registries are required in this area.

Phosphodiesterase-Type V Inhibitors

Phosphodiesterase-type V inhibitors include sildenafil and tadalafil. As expression of these enzymes is high in the lungs and the corpus cavernosum, inhibition of PDE-V results in vasodilation in these vascular beds. After oral application, sildenafil causes pulmonary vasodilation with a maximum effect after 60 min [29]. Currently there is also an intravenous formulation of sildenafil which might be an attractive option for the perioperative management of patients who are chronically treated with oral sildenafil. The effects of intravenous sildenafil start 10–15 min after infusion and last 4–6 h.

Prostacyclin Pathway

Endogenous PGI_2 results in vasodilation and has antithrombotic, anti-inflammatory and anti-proliferative effects [30]. While the prostacyclin pathway can be modulated by a variety of drugs, inhaled epoprostenol and iloprost are the most commonly used modalities in the perioperative management of pulmonary hypertension/RV dysfunction.

Inhaled Epoprostenol

Selective pulmonary vasodilation can be achieved via inhalation of PGI_2 and has been shown to be as efficacious as iNO [31] in the perioperative management of patients with pulmonary hypertension (including lung transplantation). Inhaled PGI_2 seems to be even more potent in improving pulmonary hemodynamics than iNO, while being less effective in improving oxygenation. Disadvantages of the epoprostenol solution include low stability and short half-life. It must be protected from light and is stable for only 12 h [31]. Moreover, it requires continuous nebulization. Similar to iNO, sudden withdrawal of PGI_2 can lead to rebound pulmonary hypertension.

Inhaled Iloprost

Iloprost has a longer pharmacokinetic half-life (6–9 min) with pulmonary vasodilating effects for 20–60 min, enabling intermittent nebulization [32]. While spill-over into the systemic circulation is a possibility, its effects on pulmonary vascular resistance are more profound than on systemic vascular resistance, resulting in relatively selective pulmonary vasodilation.

The use of inhaled iloprost has been described in a wide variety of cardiothoracic surgical procedures including heart and lung transplantation and in the more routine perioperative setting [33]. Iloprost inhalation requires dedicated nebu-

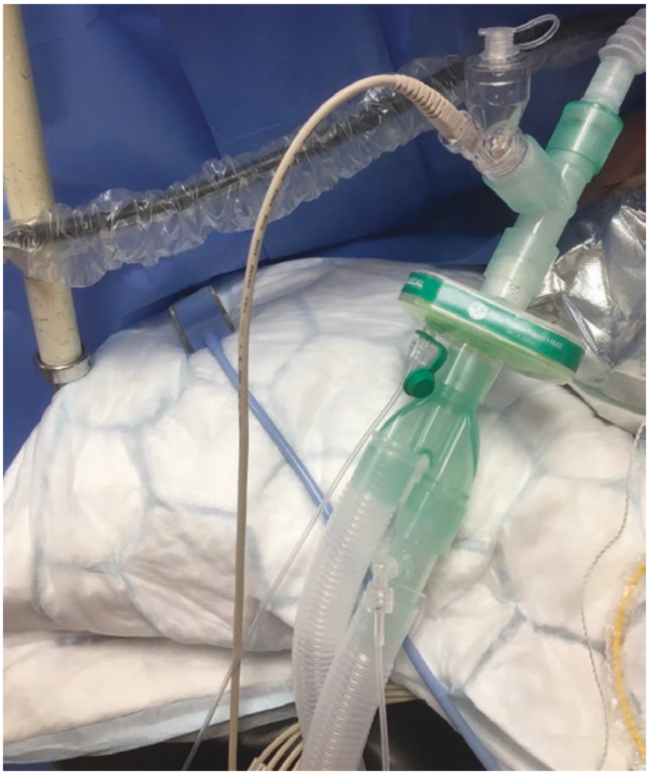

Fig. 7.2 Combined administration of inhaled pulmonary vasodilator inhaled nitric oxide (measurement port to monitor exact delivery of inhaled nitric oxide in the distal inhalation limb of the ventilation circuit but proximal to humidifying filter) and ultrasonically nebulised iloprost

lizers in order to obtain particles small enough to reach the distal alveoli (Fig. 7.2). The optimal doses for inhaled iloprost to be used in ventilated patients in the perioperative setting is unknown, but most investigators have described the nebulization of 20–40 µg iloprost. In order to maximise their efficacy, the authors of this chapter regularly combine iNO and iloprost with low dose systemic PDE inhibitors (Fig. 7.2).

Special Cardiac Surgical Settings

Coronary Artery Bypass Graft Surgery

- Routinely associated with preserved LV or mild LV dysfunction, a degree of diastolic dysfunction, mild SIRS.
- In most cases, no inotrope requirement and low dose inoconstrictor sufficient.
- Inotropes may be needed in case of preexisting severe ventricular dysfunction or inadequate myocardial preservation or prolonged myocardial ischaemia.
- Special case of emergency CABG, if failed PCI and acute myocardial infarction, dobutamine and/or PDE-type III inhibitors plus noradrenaline if hypotension.

Acute on Chronic Heart Failure

- First line is PDE-type III inhibitor with mild catecholamine inotropes (dobutamine or epinephrine) to improve stroke volume and maintain low/normal SVR.

LV Hypertrophy/Severe Diastolic Dysfunction

- Strictly to avoid inotropes.
- Vasopressors to increase SVR and maintain coronary perfusion pressure.
- Low dose PDE-type III inhibitor to specifically improve ventricular relaxation, if coexistent with moderate/severe systolic dysfunction.

Valvular Surgery

- Moderately severe aortic stenosis: avoid inotropes, low dose vasopressors.
- Chronic aortic regurgitation: depends on dilation state of LV, usually mild inotropic support if preload optimisation fails.
- Acute aortic and mitral regurgitation: aggressive inotropic support with pulmonary vasodilators in case of severe pulmonary hypertension.
- Mitral stenosis, chronic mitral insufficiency: mild inotropic support is warranted.
- Tricuspid regurgitation: Mild inotropic support, preload optimisation, RV afterload reduction.

Orthotopic Cardiac Transplantation

- Routine inotropic support to increase automaticity, biventricular contractility and RV vulnerability hence routine pulmonary vasodilation.
- Maintaining coronary and systemic perfusion pressure is vital.

Right Ventricular Dysfunction

- Frequently associated with pulmonary thromboendarterectomy, heart and lung transplantation, LVAD insertion.
- Importance of general measures to optimise PVR and RV contractility.
- Principle measures are RV afterload reduction with selective pulmonary vasodilators.
- Increase the contractile strength with inotropes (dobutamine, epinephrine and/or PDE-type III inhibitors).
- Requirement for vasopressors for maintaining coronary perfusion pressures.

The Limits of Inotropic Support, Transition to Mechanical Circulatory Support

Prolonged inotropic support is not without limitations. The current trend is institution of early mechanical support before major and potentially irreversible organ dysfunction develops. There are ever increasing options for mechanical circulatory support in cardiac surgery with principle technologies being the temporary ventricular assist devices and veno-arterial ECMO [34, 35]. Outcomes have been constantly improving for postcardiotomy mechanical support but there is debate on the timing, triggers and weaning from such support.

Conclusion

Inotropes, vasopressor and vasodilator agents have been recommended and used for several years in the treatment of cardiac surgical patients. Despite their beneficial effects in ensuring hemodynamic stability, the side effects (arrhythmias and increased myocardial oxygen consumption) may be associated with increased mortality. The pharmacodynamics of different inotropes, vasopressor and vasodilator agents suggest benefits in specific situations, but these differences have not been reflected in reduced mortality in most studies, making it difficult to formulate recommendations.

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8

Cardiac Pacing in Adults

Daniel Keene, S. M. Afzal Sohaib, and Tom Wong

High Yield Facts

- Conduction system disease may either be due to failure to generate an impulse from the sino-atrial node or failure to propagate an impulse across the atrioventricular (AV) node.
- Sinus node disease is commonly considered benign and pacing is indicated for symptoms not prognosis. High grade AV block can be fatal and irrespective of symptoms pacing is indicated.
- Postoperative bradycardia can be caused by right atrial cannulation, aortic valve disease/intervention, perioperative ischemic injury, extended cardioplegia and preoperative conduction disease.
- Epicardial placed pacing wires provide pacing support for transient bradycardia in the post-cardiac surgery setting. These leads are subject to inflammation at the wire-myocardium interface which can result in failure of the temporary lead within a week.
- Failure to pace and failure to capture are two important considerations for troubleshooting temporary pacing systems if pacing is not delivered as expected.
- Failure to pace occurs when the pacing lead does not deliver an electrical output to the myocardium. Failure to capture is when despite an electrical output the myocardium is not captured.

Introduction

Cardiac pacing is a proven and effective treatment in the management of many cardiac arrhythmias. In recent years there has been improvement in pacing technology and a marked increase in its availability. The number of patients with implanted permanent pacemakers has increased substantially in the last 20 years. Sudden cardiac death occurs in approximately 100,000 people annually in the UK [1]. Many of these deaths are due to ventricular tachyarrhythmias and may be preventable with an implantable cardioverter defibrillator (ICD) particularly in patients with poor left ventricular function [2]. Similarly, the use of bi-ventricular pacing with cardiac failure is increasing. The aim of this chapter is to give a brief overview of the aims and indications of pacing, the commonest types of implants and the role of pacing in the postoperative setting in adult cardiac patients.

Anatomy and Physiology of the Conduction System

Normal cardiac conduction requires coordinated and repetitive propagation of an electrical wave front through cardiac tissue. The sinoatrial node located in the right atrium initiates cardiac contraction. Each wave front spreads out to activate the atria. The atrio-ventricular (AV) ring electrically isolates the atria from the ventricles. The AV node though allows conduction to the ventricles passing through the bundle of His which progresses into the bundle branches. These further split into Purkinje fibres which allow rapid propagation to the ventricles (Fig. 8.1).

Indications for Pacing and Defibrillators

A defect in any element of the conduction system can result in an indication for pacing (Tables 8.1 and 8.2).

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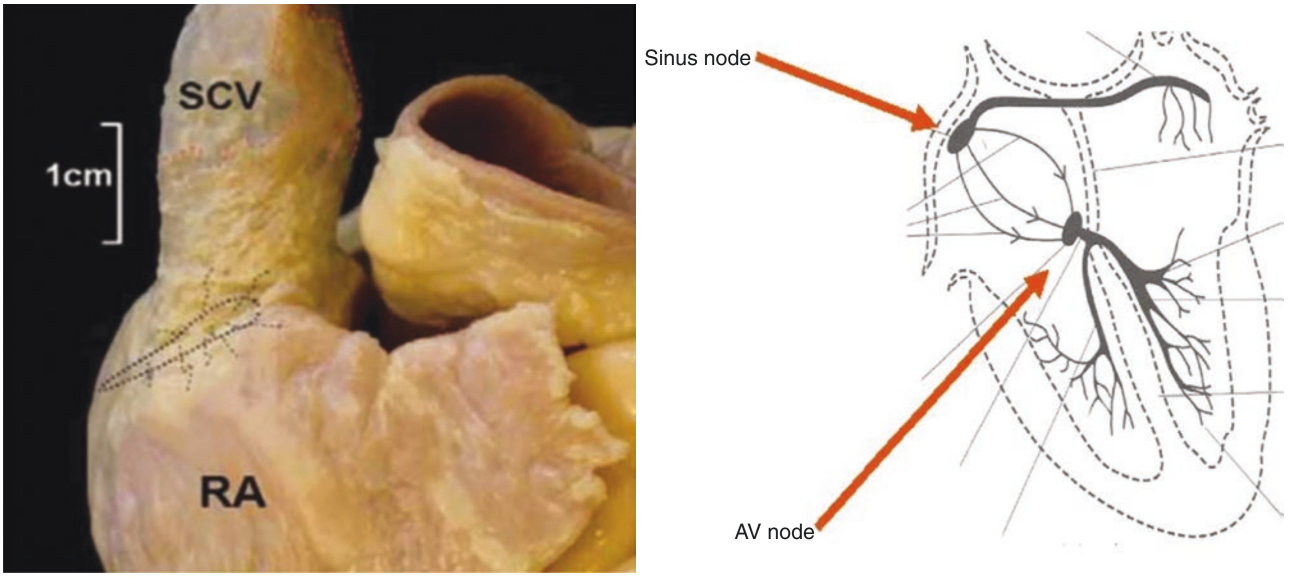


Fig. 8.1 (Left) The location of the sino-atrial node is seen close to the superior vena cava (SVC) within the right atrium (RA). (Right) The sino-atrial node is seen again, and it is from here that cardiac electrical activation begins in health. Activation spreads across both atria, but the atrio-ventricular (AV) ring isolates the ventricles and prevents this wave front from activating the ventricles. The AV node is the only electrically active connection between the atria and ventricles. The AV node allows the electrical wave front to cross the AV ring and pass along the His bundle, bundle branches and Purkinje fibres to cause coordinated and repeated cardiac contraction

Table 8.1 Indications for pacing

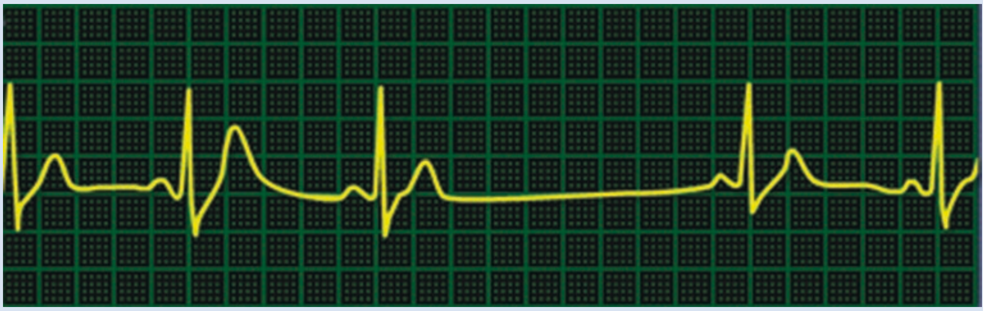
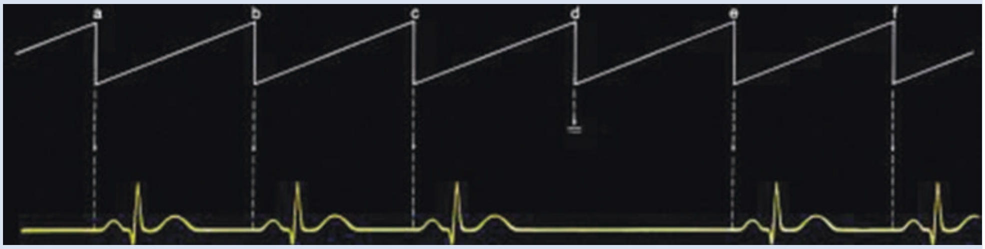
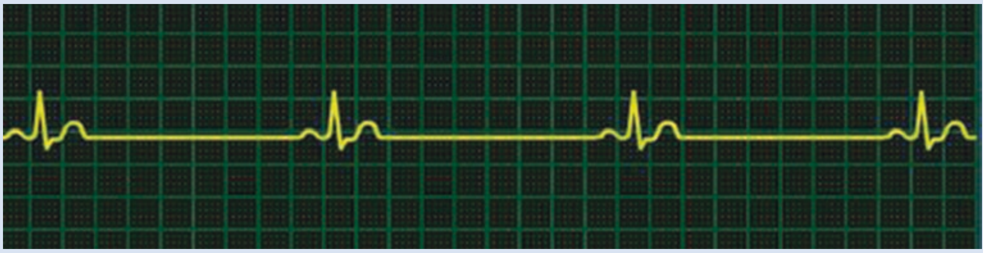
Problems with impulse formation	
Sinus arrest: Failure of the sinus node to discharge. Absence of atrial depolarisation can lead to periods of ventricular asystole.	
Sinus exit block: The ECG shows an interval between P waves which is a multiple of the normal interval. Not a random length of block.	
Sinus bradycardia: The sinus node discharges very slowly. If the patient is symptomatic and the rhythm persistent pacing may be required.	

Table 8.1 (continued)

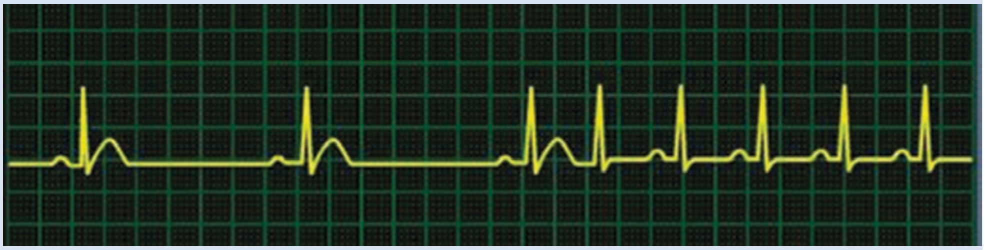
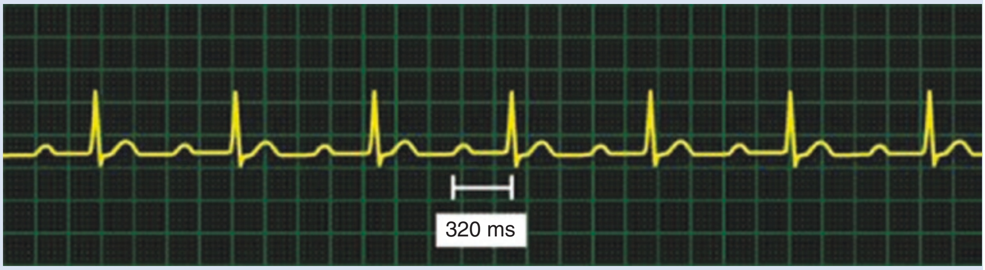
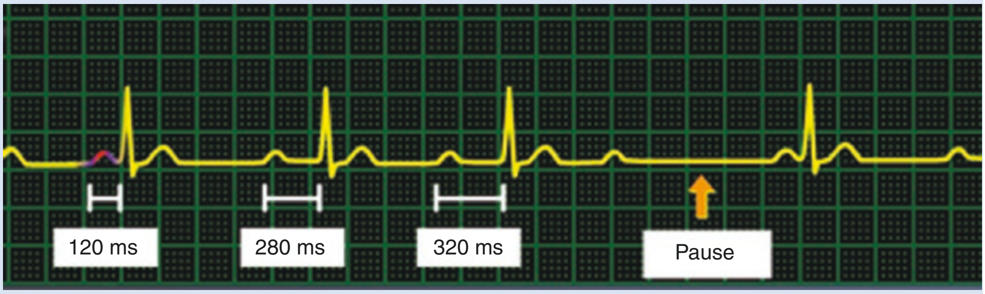
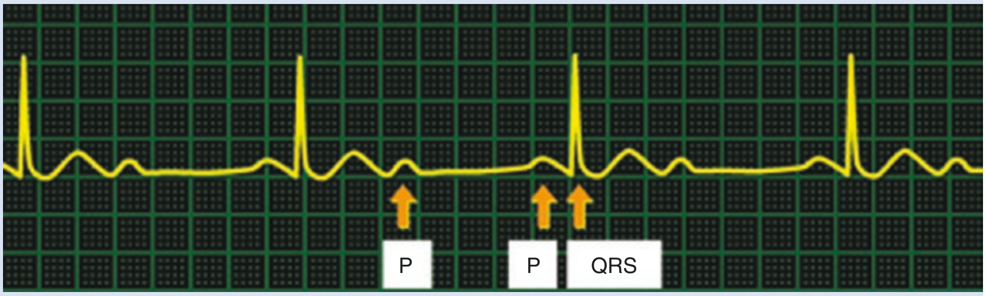
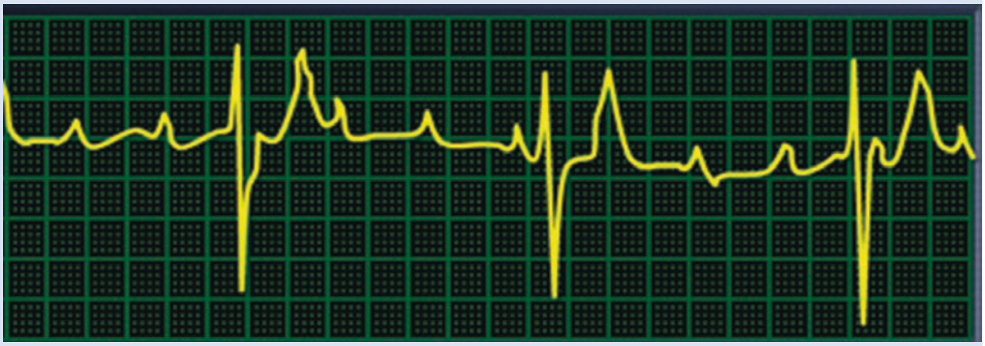
Problems with impulse formation	
Chronotropic incompetence: The heart rate is unable to change in response to the body's metabolic demand.	
Tachy-brady syndrome (Sinus node disease): intermittent episodes of slow and fast rates from the SA node (or elsewhere in the atria)—very common pacing indication.	
Problems with impulse conduction	
First degree AV block: Every P wave is conducted but the PR interval is >200 ms as a result of delayed conduction through the AV node. It is not a common indication for pacing but is not benign	
Second degree AV block (Mobitz type I): Here there is progressive prolongation of the PR interval until there is failure to conduct an atrial beat and a ventricular beat is dropped.	
Second degree AV block (Mobitz type II): Here there are regularly dropped ventricular beats. There is no change in the PR interval prior to transient failure of conduction. This is a definite indication for pacing as this has a high likelihood of progression to complete heart block (CHB).	
Complete heart block: Here there is no coordinated conduction from the atria to the ventricles. There is complete atrio—ventricular dissociation and often a wide QRS results as the ventricular complex is idioventricular in origin. Definite indication for pacing.	

Table 8.2 Guideline recommendations for pacing

Guideline recommendation	ECG findings and symptoms	
	Sinus node disease	Atrio-ventricular block
Class I (Must)	Documented symptomatic sinus bradycardia	Complete Heart Block Mobitz type II (even if asymptomatic) Symptomatic Mobitz type I
Class II (Should/Could)	Documented bradycardia in a symptomatic patient but no symptoms during documented bradycardia	Bi/Trifascicular block and symptoms reported consistent with complete heart block (Rarely) symptomatic first degree AV block
Class III (Should Not)	Asymptomatic patient with documented bradycardia	Asymptomatic first degree AV block or Mobitz type I Asymptomatic Bi/Trifascicular block
	Reversible causes: drugs/Lyme disease / metabolic/electrolyte imbalance	

Causes of cardiac conduction disease briefly include intrinsic and extrinsic causes. Intrinsic causes are mostly commonly idiopathic and degenerative (calcification), but also include ischemic heart disease (30%), or infiltrative conditions. Extrinsic causes include rate limiting drugs, increased vagal tone, infections (Lyme disease) and metabolic derangements. Conduction disease may either be due to failure to generate an impulse (problems with the sinoatrial node) or failure to propagate an impulse (problems with the AV node).

Bradycardia can lead to presyncope, syncope and injury. Sinus node disease is considered benign and pacing is indicated to improve symptoms not prognosis. High grade AV block (complete heart block (CHB) or Mobitz type II block) can be fatal and irrespective of symptoms pacing is indicated [3]. The danger of AV block is due to progression to CHB with an unstable escape rhythm. Bundle branch block does not cause bradycardia per se but can lead to dyssynchronous cardiac activation. In patients with left ventricular impairment and left bundle branch block (LBBB), positioning a pacing lead via the coronary sinus (so it activates the heart at a site on the left ventricle) can in part correct this (cardiac resynchronisation therapy (CRT)) and improves patient symptoms and prognosis [4, 5].

Defibrillators are implanted to reduce the risk of sudden cardiac death in those with a prior history of ventricular arrhythmia associated with haemodynamic compromise (secondary prevention) and those at high risk of ventricular arrhythmias (primary prevention) [3]. High risk patients include those with LV impairment (EF < 35%) or alternatively those with a diagnosis of an inherited disease (cardiomyopathy or channelopathy) which may put a patient at a high risk of sudden cardiac death. These devices can also provide pacing function whether required for bradycardia reasons or to try and improve cardiac function.

Basic Principles of Pacing

Pacing systems consist of a generator (battery) and up to three leads, with the number of leads often used to describe the type of pacemaker (single chamber (1), dual chamber (2), or biventricular pacemaker (3)) (Fig. 8.2). The system is designed to detect the underlying heart rhythm (sense) and deliver a stimulus to capture the myocardium if required (pace). In an ICD the generator includes components to allow defibrillation and leads include coils to facilitate this.

A single chamber permanent pacemaker (PPM) will usually only pace the ventricle and is often used in patients with permanent AF. A dual chamber PPM will pace the right atrium and right ventricle (Fig. 8.3). A biventricular pacemaker (CRT) will pace the right atrium, the right ventricle, and the left ventricle (via the coronary sinus).

Commonly Used Terms

Threshold

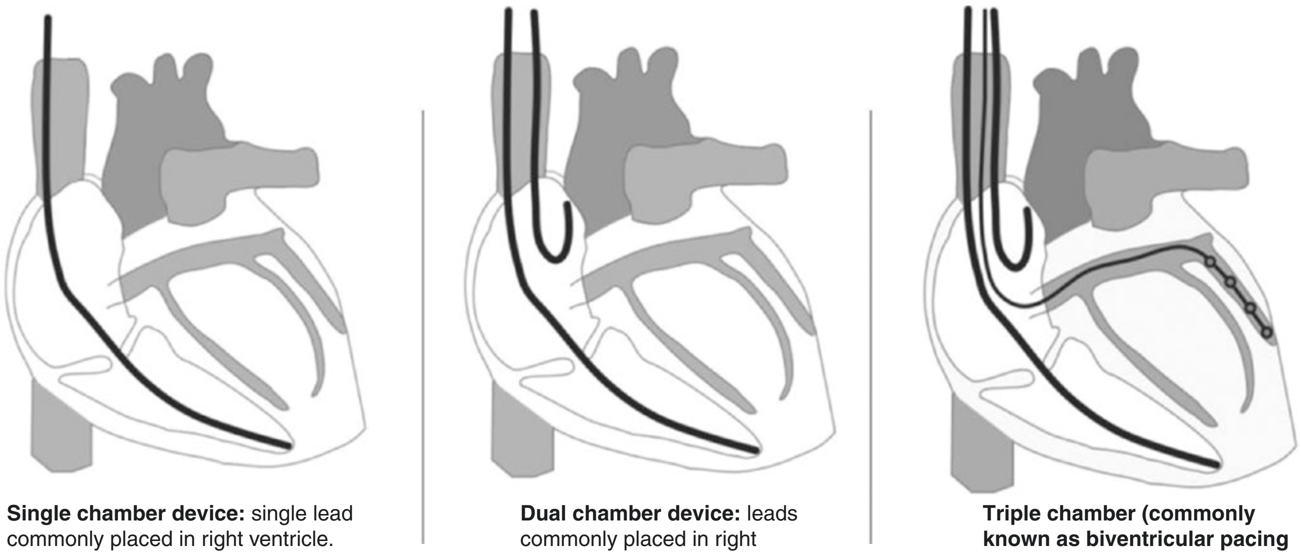
This is the minimum electrical stimulus needed to consistently stimulate the heart to provide cardiac contraction. It must be large enough (voltage) for a long enough (pulse width) period to cause depolarisation of the myocardium. The output delivered by a pacing device must have an adequate safety margin, usually twice the threshold.

Sensitivity

In order for a pacemaker to know whether it needs to deliver a pacing stimulus (i.e., if an intrinsic heart beat is missing) the pacemaker must be able to “see” the hearts intrinsic electrical signals. “Sensing” is the ability of the pacemaker to detect cardiac electrical signals (measured in millivolts). Any electrical activity below the set value for the sensitivity is ignored. This helps to prevent sensing of T waves or far field signals from the chamber not being paced which would otherwise inhibit pacing (Fig. 8.4).

Implantation Techniques

Pacemakers and ICDs are usually implanted under local anaesthesia. Depending on procedure type, implantation typically takes 45–120 min. Pacemakers are typically



Single chamber device: single lead commonly placed in right ventricle. Occasionally single lead placed in right atrium.

Dual chamber device: leads commonly placed in right atrium and right ventricle.

Triple chamber (commonly known as biventricular pacing or cardiac resynchronization therapy): leads placed in right atrium and then the right ventricle and coronary sinus to activate the left ventricle.

Fig. 8.2 Types of pacemaker

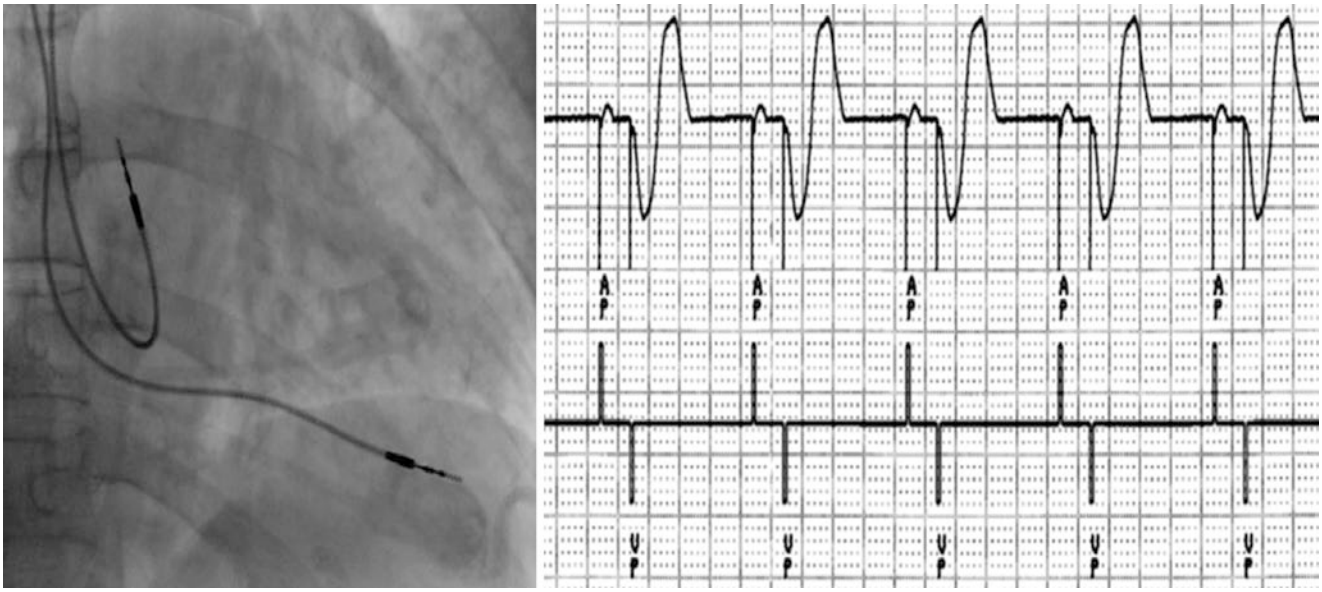
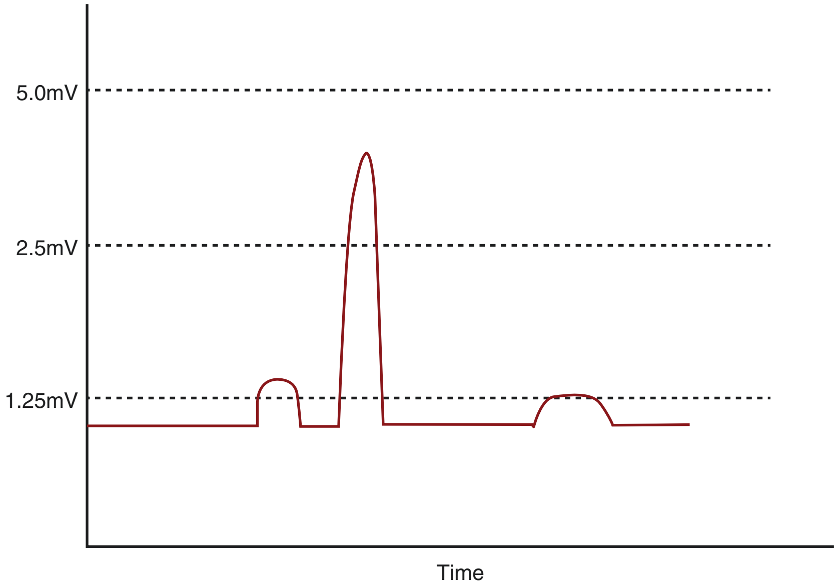


Fig. 8.3 A dual chamber pacemaker

implanted on the left side of the chest wall through a 4–5 cm incision made horizontally approximately 2 cm infraclavicularly. Dissection down to the pre-pectoral plane is performed and within this plane a pocket fashioned for the device. Venous access is then obtained via a cephalic vein following cut down and venotomy or puncture of the axillary or subclavian vein. Sheaths positioned using a Seldinger technique are used to deliver the leads to their appropriate position. Leads are fixed to the myocardium using either an active fix screw or tines (small hooks) that passively grip the lead to the heart muscle. Once the leads are in situ the electrical (sensing and capture) parameters are checked. The leads are secured in place to muscle with sutures prior to connecting to the generator and closing the wound [6, 7].

Fig. 8.4 Pacemaker sensitivity



Sensitivity can be explained with this image. At a sensitivity level of 5.0mV no cardiac signals are seen. At a sensitivity level of 2.5mV only the QRS electrogram signal is seen. At a sensitivity of 1.25mV the P wave, QRS and perhaps T wave would be sensed. This would mean for a ventricular lead this amount of sensitivity is too great.
A pacemaker interprets all signals as QRSs if it is a ventricular lead or as P waves if an atrial lead. If programmed with a sensitivity of 1.25mV and this was a ventricular lead — the pacemaker might think there were three QRSs when in fact there is only one.
The lower the programmed number the greater sensitivity and more electrical signals will be seen.

Common Complications and Problems with Devices

Venous thrombosis occurs peri-procedurally in 1/50 cases affecting the ipsilateral arm. This may cause swelling in the arm, but it usually settles in a few days and is rarely a serious problem.

Pacemaker infection: 1% of patients will develop an infection post implant. This almost always requires removal of the whole system to reduce the risk of endocarditis.

Pneumothorax: 1% of patients during pacemaker implantation will suffer a pneumothorax when venous access for the leads is attempted. This is more common with subclavian access. Management is guided by the size of the pneumothorax and the clinical status.

Pericardial effusion/tamponade: Positioning pacing leads can lead to the development of a pericardial effusion. This can be asymptomatic, and no intervention is required as the perforation spontaneously repairs itself. However, for 1/500 cases a pericardial drain is required.

Lead displacement: In 1% of patients leads displace. This usually occurs within the first 6 weeks prior to fibrosis occurring around the lead. Lead displacement in a pacing dependent patient may lead to development of presyncope or syncope as the lead may fail to sense missed events or fail to capture myocardium when pacing is attempted.

Long term lead complications: Over time leads can become damaged, eventually leading to the leads failing to capture, or in the case of ICD leads where noise is inappropriately detected as VT/VF, inappropriate shocks. This is usually manifested early on as falls in the impedance when the insulation is damaged or rises in the impedance when the lead is beginning to fracture [8].

Novel Device Approaches

His Bundle Pacing

Pacing the His bundle has recently emerged as a method for delivering more physiological pacing. This approach has been demonstrated to be safe and feasible even in patients with distal infra-hisian block and can also reverse bundle branch block [9, 10]. Large randomised controlled trial (RCT) data is awaited to demonstrate its superiority over both RV pacing or even biventricular pacing.

Leadless Pacing

Leadless pacing systems have been developed which can avoid the complications of conventional transvenous system. The Micra (Medtronic) is an example of a, transcatheter,

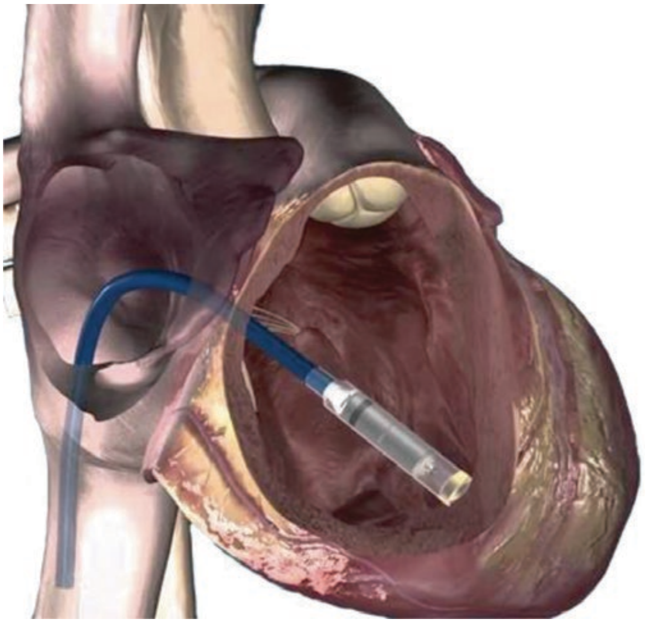


Fig. 8.5 Deployment of a leadless pacemaker

single chamber ventricular pacemaker (Fig. 8.5). The capsule has tines at the end that allow it to attach to right ventricular endocardium. For now it can only function as a single chamber ventricular pacemaker but this technology is likely to evolve [11].

Subcutaneous ICDs

Subcutaneous ICDs have emerged as an alternative to transvenous defibrillators to avoid complications of transvenous devices. These are particularly useful if there is no additional pacing indication. The defibrillator lead is tunnelled subcutaneously lateral to the sternum and then across to the left axillary region where it is connected to the generator [12] (Fig. 8.6).

WiSE CRT

The WiSE CRT system is an endocardial leadless option for left ventricular pacing (Fig. 8.7). This can be used where conventional LV pacing cannot be performed via the coronary sinus. The device requires an extended period of dual antiplatelets or anticoagulation. Randomized controlled trials are needed to assess long-term clinical outcomes, and further advances are needed for selecting the optimal endocardial location for pacing [13].

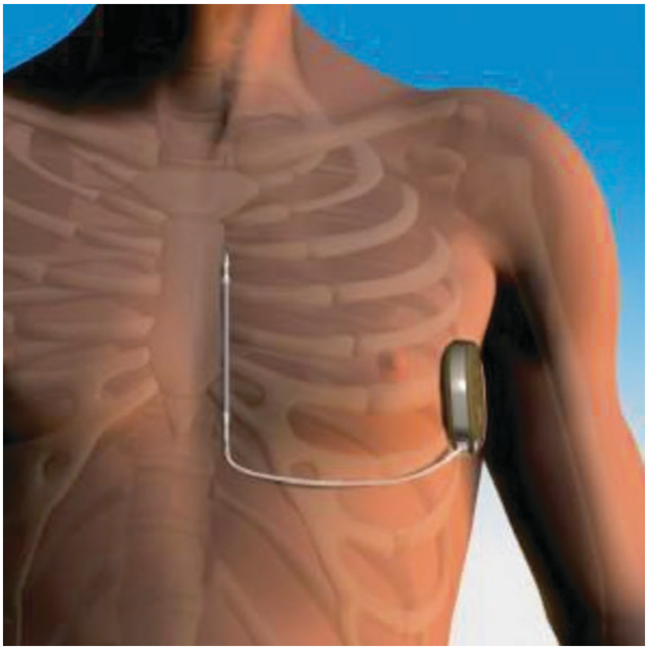


Fig. 8.6 A subcutaneous implantable cardioverter defibrillator (ICD). This image shows the location of the ICD generator. It is often positioned underneath the latissimus dorsi muscle and the lead passed subcutaneously utilising 2–3 small skin incisions so that it runs inferior to the heart and then superior to the left side of the sternum. These devices cannot deliver long-term pacing to patients

Perioperative Management of Devices

Pacemakers and ICD generators have filters to minimise the effect of electrical and magnetic interference. However, if the interference is of a magnitude or frequency which cannot be filtered it can potentially cause inhibition of pacing, induction of a fixed rate pacing, software reset or inappropriate ICD shocks. Electromagnetic interference will usually only have a transient effect on device function. Very powerful fields (e.g., gamma radiation) may have permanent effects [14–16].

When surgical diathermy/electrocautery is to be used remote from the implanted device, there is only a low risk of problems. Bipolar diathermy reduces the risk compared to unipolar. Other precautions include limiting diathermy use to short bursts and placing the return electrode away from the device so the components are kept away from the diathermy circuit [17, 18].

If detectable pacemaker inhibition occurs during diathermy, the surgeon should either discontinue diathermy, use shorter bursts or the device should be programmed in an obligatory pacing mode (e.g., VOO).

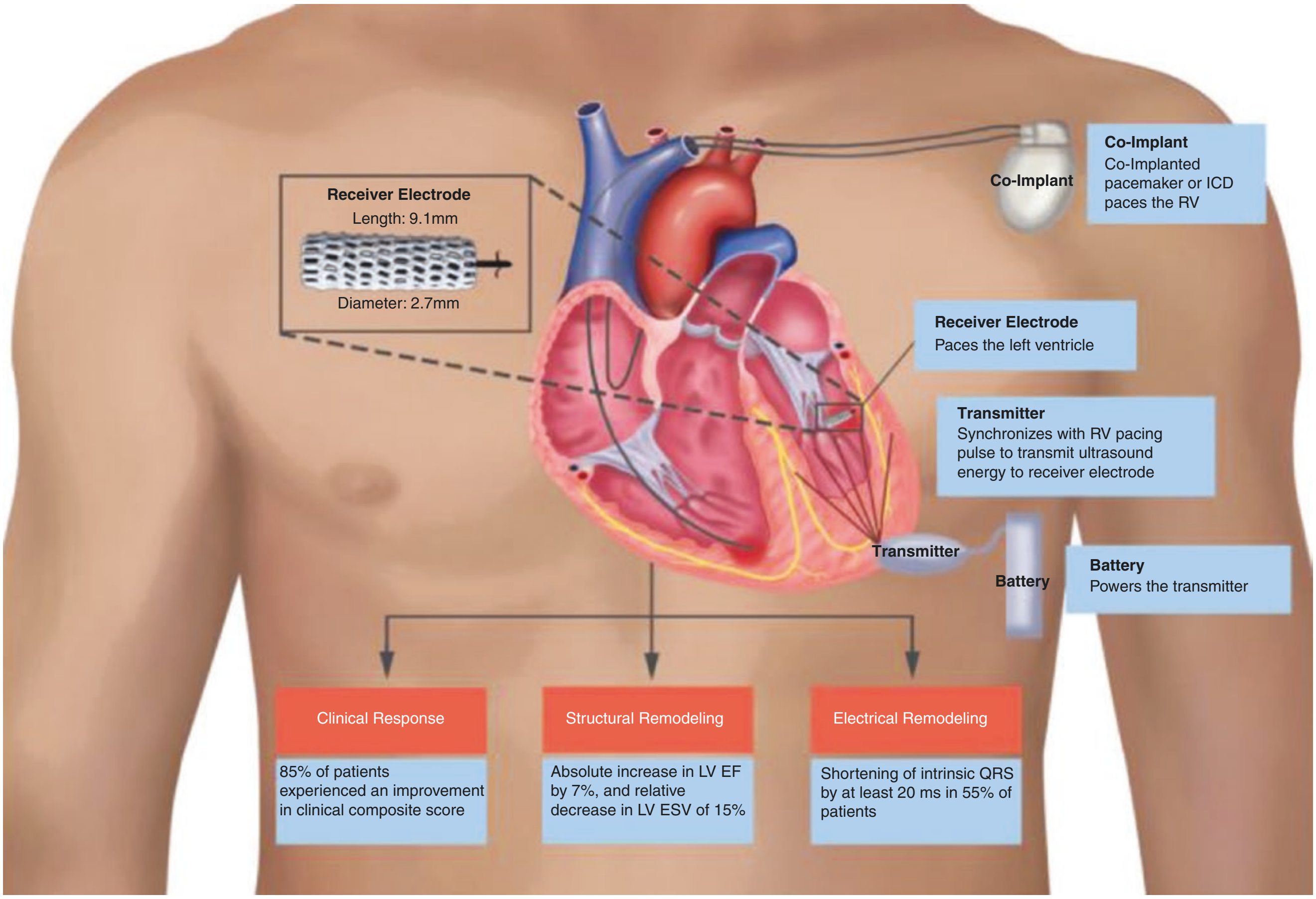

Receiver Electrode
Length: 9.1mm
Diameter: 2.7mm
Co-Implant
Co-Implant
Co-Implanted pacemaker or ICD paces the RV
Receiver Electrode
Paces the left ventricle
Transmitter
Synchronizes with RV pacing pulse to transmit ultrasound energy to receiver electrode
Transmitter
Battery
Battery
Powers the transmitter
Clinical Response
85% of patients experienced an improvement in clinical composite score
Structural Remodeling
Absolute increase in LV EF by 7%, and relative decrease in LV ESV of 15%
Electrical Remodeling
Shortening of intrinsic QRS by at least 20 ms in 55% of patients

Fig. 8.7 WiSE cardiac resynchronization therapy (CRT) system. The pacing system consists of a receiver electrode and an ultrasound transmitter which is battery powered. The transmitter detects when standard right ventricle (RV) pacing is delivered from a co-implanted pacemaker. The transmitter then transmits ultrasound energy to a receiver electrode, which is implanted in the left ventricular endocardium. The receiver electrode converts the ultrasound energy into an electrical pacing impulse. The effects are shown in the diagram. *ESV* end systolic volume, *ICD* implantable cardioverter defibrillator. (Reproduced from Reddy et al. J Am Coll Cardiol 2017;69:2119–2129 [13]. Copyright © 2017 American College of Cardiology Foundation. Published by Elsevier Inc.)

MRI and Pacing

There is potential for MRI-induced cardiac lead heating and movement which may alter pacing properties (inappropriate sensing/activation of the device) or even damage the myocardium [19]. This concern has previously limited those patients with a pacemaker from having an MRI. Many modern pacemakers (post 2008) can now safely withstand standard MRI scanning movement if a set of specified MRI conditions are met. Often the device needs to be reprogrammed prior to the patient undergoing the scan. Most scanning centres insist that there are no redundant pacing leads and that the devices and leads have been manufacturer approved as MRI compatible. That said, there is increasing evidence that even those with non-MRI-conditional devices can safely undergo MRI scans [20].

Pacing in the Peri- and Post-operative Setting

Peri-operative and Post-operative Pacing in Cardiac Surgery

Epicardial pacing wires are placed during surgery to provide pacing for transient bradyarrhythmia post-cardiac surgery. These are usually placed on the ventricles and the atria.

The wires are embedded in the myocardium and then tunnelled through the body wall to bring the wire to the skin surface. The leads need to be sufficiently well anchored in the myocardium to avoid premature dislodgement whilst allowing removal by gentle traction alone. In the immediate post-operative period patients with pacing need are often left to pace at 60–80 beats per minute to try and maximise cardiac output. When weaning from pacing to intrinsic cardiac rhythm often a period of "back-up" pacing is programmed at ~40 bpm. If further pacing is required, it can be commenced safely.

Epicardial wires are subject to an inflammatory reaction that effects the wire-myocardium interface. This process is usually accelerated with delivery of higher energy pacing. Unfortunately, the only remedy for increased resistance (apart from siting a new pacing lead often via a transvenous approach) is the application of increased current or voltage—which further increases the inflammation. Epicardial wires often fail to sense and/or capture within a week. Increases in stimulation threshold typically occur after 5 days. Failure to pace has been observed in >60% of atrial wires after 5 days [21, 22].

The daily checks required are outlined in Table 8.3.

Troubleshooting Temporary Epicardial Systems

If pacing is not being delivered as expected, failure to pace and failure to capture should be considered as causes.

Failure to pace occurs when the pacemaker lead does not deliver an electrical output to the myocardium. No pacing spikes are seen on the ECG, and the heart rate is lower than the pacing rate. Causes include an unstable connection between lead and generator; battery depletion, oversensing or cross-talk (where electrical signals are misinterpreted as P waves or QRS complexes resulting in inhibition of pacing delivery).

Failure to capture occurs when there is electrical output from the device and lead (pacing spikes seen) but myocardium is not captured. Causes include acute fibrosis around the pacemaker lead, ischaemia; metabolic imbalance, and drugs including flecainide.

Progressively increasing thresholds is often a sign of impending loss of capture. To avoid this, reversible causes should be corrected. Reversing the polarity of the lead or switching to a unipolar approach with positioning of a subcutaneous patch could be considered. These are usually temporary solutions and alternatives are often required (i.e., temporary transvenous pacemaker, or implant of a permanent system) [21, 22].

Transitioning to Permanent Pacing in the Post-operative Period

Post-operative conduction disorders can affect up to ~25% of patients in some series. Optimal timing for PPM insertion in the post-operative setting has not been clearly defined due to the relatively poor understanding of the natural history of post-operative conduction disturbances. There is significant variability in how pacemaker dependency is assessed and defined. Of the 5% of patients who receive permanent pacing the long-term pacing dependency rates reported in the current literature vary from 32 to 91% [23].

The risks and costs of permanent pacemaker implantation (which may not be necessary) need to be balanced against the prospects of a prolonged hospital stay with epicardial wires.

Numerous causes contribute to postoperative bradycardia (Table 8.4, Fig. 8.8).

Existing guidelines reflect the lack of evidence and consensus in this area. Guidelines provide a class I indication for PPM implantation in "postoperative atrioventricular block

Table 8.3 Daily checks required on epicardial leads

Underlying rhythm	The presence of a stable rhythm will determine the need for ongoing pacing requirements	This is best done by turning down the pacing rate and watching for the intrinsic rhythm to appear (or to turn down the pacing output until capture is lost but this may be limited if there is no underlying rhythm).
Sensitivity	This is a number (measured in mV) representing the minimum current (electrical activity) that the pacemaker is able to sense The lower the number programmed means greater sensitivity and more electrical signals will be seen	To check sensitivity the pacemaker rate should be programmed below the intrinsic heart rate if present and the sensitivity number then turned down (making the pacemaker more sensitive) until the sense indicator notes each intrinsic depolarisation (in time with the P or R wave on the surface ECG). The number at which this first occurs is the sensitivity threshold. It is recommended to set the pacing generator at half this threshold, to allow for detection of abnormally small signals, and for the possibility that progressive lead fibrosis over the course of the day will reduce the current transmitted to the pacemaker. If there is no endogenous rhythm, it is impossible to determine the pacemaker sensitivity, in which case the sensitivity is typically set to 2 mV.
Capture threshold	This is the minimum energy output required to stimulate an action potential in the myocardium	The capture threshold should not be checked if there is no underlying rhythm for fear of losing capture and not being able to regain it. If this is the case, careful continuous attention should be paid to the development of occasional missed beats, which will indicate a rise in the capture threshold and a need to increase the pacing output further or find an alternate means to safely activate the heart. If safe to check the pacing threshold, the pacemaker rate should be set above the patient's intrinsic rate, so that the chamber of interest is consistently paced. The pacemaker energy output is then reduced until a QRS complex no longer follows each pacing spike. This is the capture threshold. Typically, the output is left at twice the threshold this allows a margin of safety.

Table 8.4 Causes of postoperative bradycardia

Right atrial cannulation for cardiopulmonary bypass	May cause sinus node dysfunction but usually resolves within 7 days [23, 24].
Aortic valve disease/ Intervention	Particularly calcific aortic valve stenosis is often associated with underlying conduction disease even if not overtly apparent on a surface ECG. The aortic valve sits in close proximity to the bundle of His and local damage to this structure may be to blame for increased conduction disease. Damage may be caused by trauma including laceration of conduction system fibres by sutures used to anchor the valve prosthesis or pressure from residual calcific material and impingement of the prosthetic valve seat on conduction tissue. This could be the mechanism for conduction disease even in sutureless valve surgery [24–26].
Peri-operative ischemic injury	Ischemic injury to the conduction tissue can contribute to a transient need for pacing, most likely facilitated by left main or proximal LAD artery disease. There has been no independent association between coronary artery disease and late pacemaker dependency however [23].
Other peri-operative factors	Extended duration of cardioplegia may contribute to the incidence of heart block postoperatively. The longer the duration the greater the exposure to the high concentration of potassium ions in cardioplegic solution which raises extracellular potassium concentration in the conduction tissue reducing the automaticity of the AV nodal cells and suppressing the excitability and conductivity of the conduction system leading to increased pacing needs immediately post-operatively and in a single study long-term pacemaker dependency [27].
Patient factors	Preoperative conduction disease has been shown to predict postoperative pacemaker dependency particularly those with first degree AV block and QRS duration >120 ms [28].

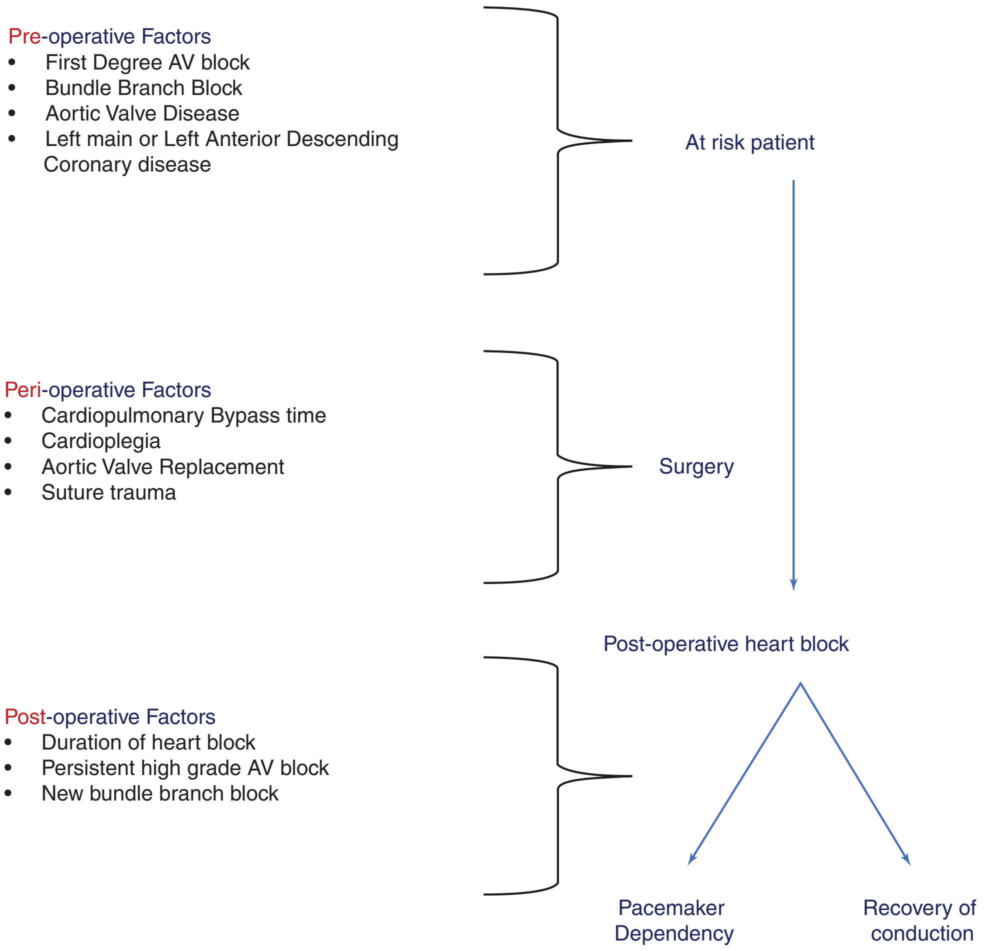

Pre-operative Factors
• First Degree AV block
• Bundle Branch Block
• Aortic Valve Disease
• Left main or Left Anterior Descending Coronary disease
At risk patient
Peri-operative Factors
• Cardiopulmonary Bypass time
• Cardioplegia
• Aortic Valve Replacement
• Suture trauma
Surgery
Post-operative heart block
Post-operative Factors
• Duration of heart block
• Persistent high grade AV block
• New bundle branch block
Pacemaker Dependency
Recovery of conduction

Fig. 8.8 Diagram highlighting pre-operative, peri-operative and post-operative factors that may lead to a patient needing a pacemaker after cardiac surgery

that is not expected to resolve", however there are no recommendations regarding identification of the patients at higher risk for delayed or non-resolution of post-operative block [29]. If adopting a conservative approach to permanent pacemaker insertion a waiting period of 5–7 days may be reasonable. Beyond this, epicardial wires may begin to fail.

Cardiothoracic Surgeon Involvement in Pacing Procedures

There are two procedures, discussed below, where cardiothoracic surgeons work closely with cardiologists in pacing procedures.

Surgical Lead Implantation

The most common approach for lead placement is transvenous. However, with venous occlusions or multiple leads overcrowding and impeding blood flow alternative solutions are often required. Furthermore, in cardiac resynchronisation therapy, there are occasions where there is unfavourable coronary sinus anatomy for positioning the left ventricular lead. In these situations, surgical epicardial pacing lead placement can be considered.

If concomitant cardiac surgery is being performed the leads are placed at the end of case. If the leads are affixed to the heart in areas of bare muscle not covered with epicardial fat or scar, contact and electrical conditions are usually very good. Epicardial leads are usually of a sew-on or screw-in type, (commonly bipolar sew-on atrial leads and bipolar screw-in ventricular leads). If left ventricular pacing is required, the lead should be targeted to the lateral or posterolateral basal left ventricle between the first and second obtuse marginal coronaries. In general, available epicardial lead systems demonstrate decreased longevity and worse chronic lead performance compared with endocardial pacing [30, 31].

Lead Extraction

Device infections and in many cases lead failure will necessitate lead extraction. Leads that have been in for >1 year can adhere due to fibrosis within the heart and the vascular tree. A percutaneous extraction is normally attempted first. This may involve traction-counter traction approaches using a locking stylet and mechanical extraction tool or the use of a laser sheath to free a lead from fibrotic adherence.

Lead extraction may be performed in either a specialized cardiac catheter laboratory or in cardiac theatres. Regardless of the venue, equipment, and personnel needed to perform emergency surgery and cardiopulmonary bypass should be aware and available if needed. The risk associated with percutaneous extraction are highlighted in Table 8.5 [32]. A surgical approach may be required if percutaneous techniques fail. Primary thoracotomy should also be considered when there is a large lead vegetation (>2.5 cm) or a vegetation associated with the lead and a right-to-left intracardiac shunt [33].

Death and major complications often result from vascular tears or cardiac perforation. A tear in the SVC can lead to rapid life-threatening haemorrhage and requires immediate surgery. Occlusion balloons exist to rapidly stem blood loss as a bridge to surgical intervention [34] (Fig. 8.9).

Table 8.5 Risks associated with percutaneous extraction

Reported frequency	
Major	
Death	0.8%
Cardiac tamponade	1.4%
Haemothorax	0.4%
Pulmonary embolus	0.1%
Lead ragment migration	0.1%
Total major complications	1.9%
Minor	
Perforation	0.4%
Myocardial Avulsion	0.1%
Venous Avulsion	0.1%
Other	0.9%
Total minor complications	1.4%
Any complication	3.3%

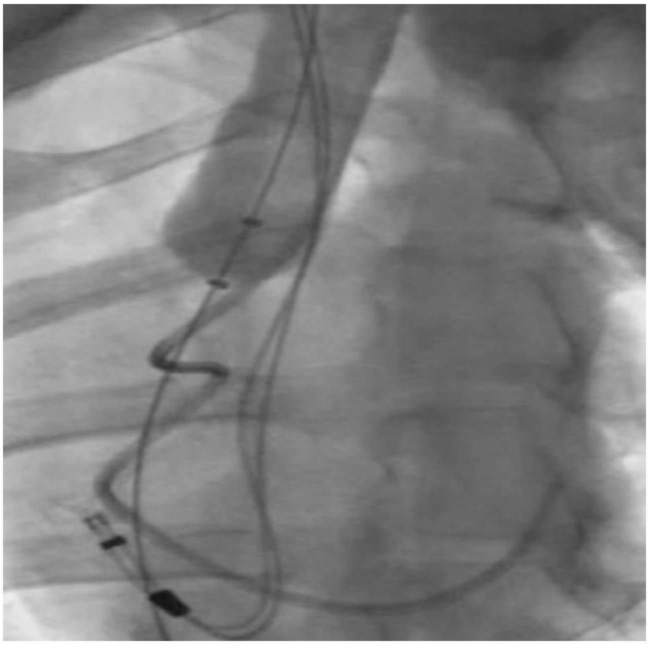


Fig. 8.9 Radiographic image of an occlusion balloon having been deployed to tamponade a superior vena cava tear. This is done to allow time for a surgeon to perform emergency surgery

Conclusion

Cardiac pacing and arrhythmia management are of paramount importance in the peri- and post-operative setting. Whether or not arrhythmia is the primary concern, the cardiothoracic surgeon needs to be proficient in arrhythmia recognition, temporary pacing, and basic device troubleshooting of previously implanted cardiac devices. At the same time with increasing numbers of implants, close collaboration is required between cardiologists and cardiac surgeons for implants and extraction.

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Adult Cardiopulmonary Bypass

9

Demetrios Stefanou and Ioannis Dimarakis

High Yield Facts

- A core understanding of how cardiopulmonary bypass (CPB) works in order to provide adequate organ perfusion and gas exchange is essential.
- The circuit consists of a tubing network for circulating blood to and from the patient, a pump, heat exchanger, reservoir, sump suction and cardioplegia lines.
- The surgeon can design with the perfusionist the routes of arterial and venous cannulation, as well as choose the appropriate myocardial protection strategy, according to the operation.
- Versatile myocardial protection techniques exist to facilitate different operative procedures.
- The current trend is to use normothermia and selective cerebral perfusion.
- Adjuncts such as tube coating or anti-inflammatory strategies can be used under certain circumstances.
- A range of CPB modifications have enabled developments in minimally invasive and more complex cardiac surgery.

Introduction

The evolution of operative approaches and techniques in cardiac surgery has been linked with parallel developments in our understanding and application of cardiopulmonary bypass (CPB), first introduced in 1953, in order to provide an arrested heart and a bloodless field [1].

The original concept of supplying mechanically assisted blood flow and gas exchange (oxygen delivery and carbon dioxide elimination), remains central in modern cardiac surgical practice, and has enabled its spread from adult and paediatric operations, to a host of heart failure and minimally invasive approaches both during standard operative periods and longer periods of circulatory or ventilatory support. The latter applications of this technology include ventricular assist devices (VAD), and extracorporeal membrane oxygenation (ECMO) that are evolutions of the central concept of CPB.

The central concept involves linking the patient's circulation, with a primed CPB circuit of tubing and active biomaterial surfaces, such as oxygenators and filters (Fig. 9.1). The tubing is usually made of polyvinyl chloride admixed with a large quantity of plasticizer; the latter may contribute up to 80% of the mass of tubing [2].

Cannulation Strategies

Preoperative planning involves selection of appropriate cannulae to connect the arterial and venous limbs of the CPB circuit to the patient. This involves multiple considerations including patient size, anatomy, and procedure to be undertaken.

Arterial inflow options include:

- The ascending aorta.
- The arch vessels including the innominate and carotid arteries directly, or via synthetic grafts.
- The axillary artery directly, or via synthetic grafts.
- The femoral artery directly, or via synthetic grafts.
- The left ventricular apex, in emergent situations.

The ascending aorta remains the most common site of arterial cannulation due to easy access following median sternotomy. In more complex scenarios including redo surgery and aortic dissection other sites may be selected. Furthermore, innominate, carotid, or axillary cannulation may also be used for antegrade cerebral perfusion, during periods of circulatory arrest. This requires flows of 10–20 ml kg^{-1} min^{-1}.

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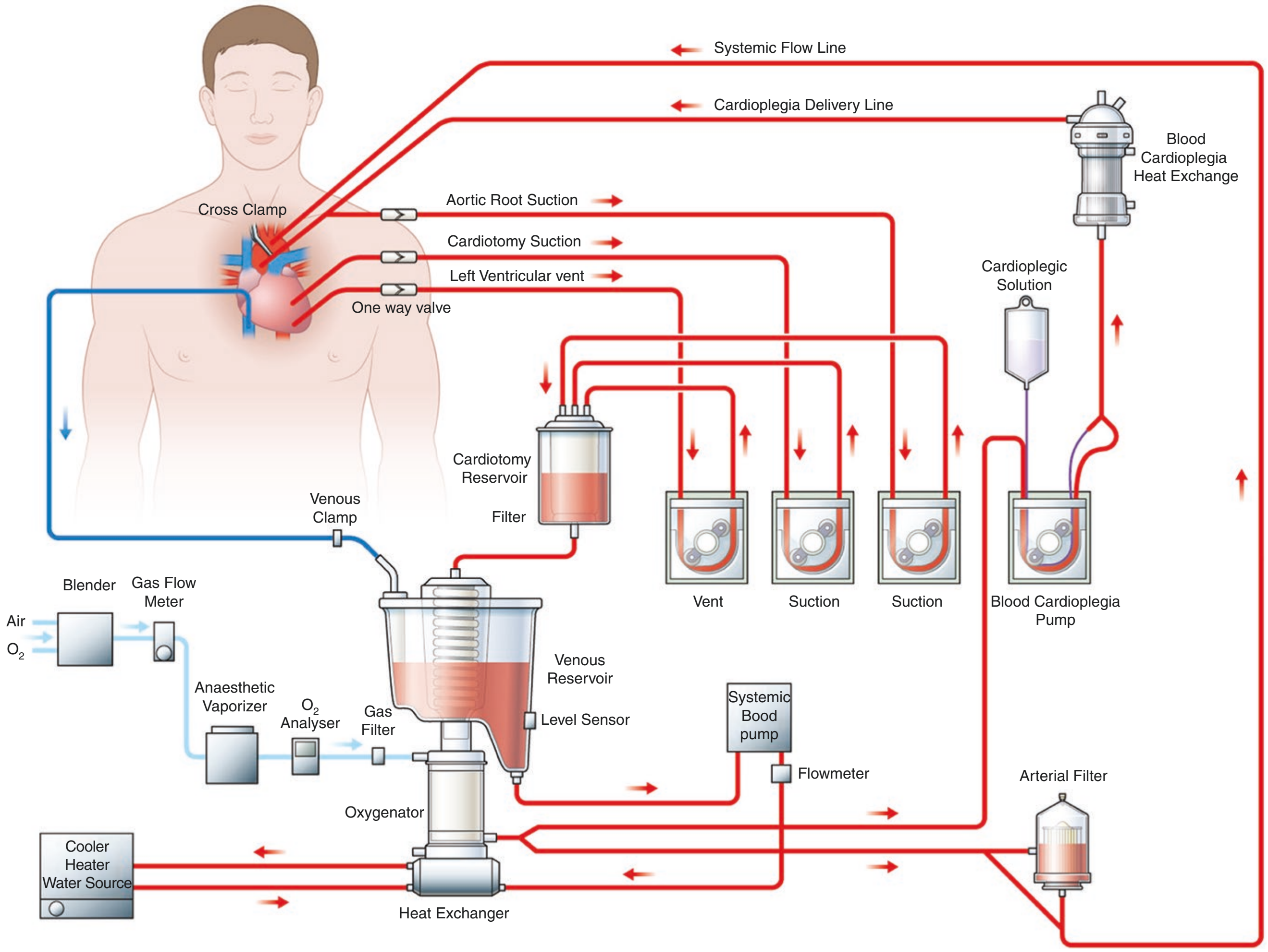
Systemic Flow Line
Cardioplegia Delivery Line
Blood
Cardioplegia
Heat Exchange
Cross Clamp
Aortic Root Suction
Cardiotomy Suction
Left Ventricular vent
One way valve
Cardioplegic
Solution
Cardiotomy
Reservoir
Filter
Venous
Clamp
Vent
Suction
Suction
Blood Cardioplegia
Pump
Blender
Gas Flow
Meter
Air
O_2
Anaesthetic
Vaporizer
O_2
Analyser
Gas
Filter
Venous
Reservoir
Level Sensor
Systemic
Bood
pump
Flowmeter
Arterial Filter
Oxygenator
Cooler
Heater
Water Source
Heat Exchanger

Fig. 9.1 The cardiopulmonary bypass circuit

During deep hypothermia and arrest, retrograde cerebral perfusion can be achieved via an arterial inflow side arm, connected to the superior vena cava or internal jugular vein at 300–500 ml/min and pressures of 15–25 mmHg.

Venous drainage is usually via:

- The right atrium and superior vena cava. The cannulae most commonly used are two-stage allowing for cavo-atrial drainage. In cases where the inferior vena cava is not amenable to cannulation a single Ross basket device may be used. Three-stage cannulae also exist that permit drainage even when the right atrium is collapsed.
- Both vena cavae (bicaval cannulation), for intracardiac surgery or transplantation, utilizing two venous straight or right-angled single-stage cannulae.
- The femoral vein.
- The internal jugular vein.
- Combinations of the above. For example in minimally invasive/port access surgery jugular and femoral vein cannulation are both employed.

Venous drainage from the patient is returned to a venous reservoir, which can be made of hardshell polycarbonate, or soft polyurethane. Drainage can be gravity-assisted with siphoning or vacuum-assisted with a negative pressure of −20 to −50 mmHg or active with the use of a centrifugal pump.

During deep hypothermia and arrest, retrograde cerebral perfusion can be achieved via an arterial inflow side arm, connected to the superior vena cava or internal jugular vein at 300–500 ml/min and pressures of 15–25 mmHg.

Venting contributes toward a bloodless field, and avoids deleterious myocardial distension. It also helps removing air form the cardiac chambers, especially during weaning from CPB. It can be achieved most commonly via:

- The ascending aorta, coupled with a delivery system for antegrade blood cardioplegia.
- The right superior pulmonary vein, toward the left ventricle.
- The pulmonary artery.

Unfractionated heparin (3–5 mg kg^{-1}), is administered to maintain an activated clotting time (ACT) >400 s. The ACT is monitored throughout CPB and also during the reversal of heparin with its antidote protamine. Protamine is usually given at a dose of 1–1.3 mg per 100 units of heparin used.

Lysine analogues (e.g., tranexamic acid, ε-aminocaproic acid) are frequently used to reduce fibrinolytic haemorrhage.

Key Elements of the Cardiopulmonary Bypass Machine

Drained venous blood is stored in the reservoir, at a level of safety, which together with the presence of polyester filters and polyurethane de-foamers, ensures no air or debris are inadvertently entrained into the arterial limb of the CPB circuit. In this reservoir, bloodshed in the operating field can also be returned via sump suckers.

From the reservoir, the blood is then forwarded via an arterial filter to an oxygenator, which acts as an artificial lung, where oxygen delivery and carbon dioxide elimination, take place via a connection to a gas line. Microporous polypropelene hollow fiber membrane oxygenators have replaced bubble oxygenators. They provide an interface for safe gas exchange, minimising the risk of micro emboli. Majority of oxygenators incorporate a heat exchanger. That provides circulatory temperature control that ranges from the patient's normal temperature (normothermia), down to deep hypothermia.

Arterial line filters are also designated for further protection against microaggregate embolisation, containing pores of 40 μm in diameter. They are divided into screen and depth filters and are made of materials such as polyester, nylon or wool. Their function is the product of either permeability related directly to pore size, or retention of foreign material through exposure of circulating blood to a complex mesh of biomaterials. Some arterial filters, are heparin-coated, in order to improve biocompatibility.

Kinetic energy for circulation during CPB, can be provided with 2 types of pumps, roller and centrifugal.

Roller pumps**,** where the first type used in cardiac surgery. A pair of rotating heads compress in sequence, the CPB tubing in an antegrade direction toward the patient when arterial inflow is concerned, or in a retrograde direction, in the case of sump suckers.

Centrifugal pumps**,** function through vortexing blood. Centrifugal forces are generated through a magnetic field. Blood flow depends on pressure and resistance within the CPB circuit. They are increasingly being used in both cardiopulmonary bypass as well as ECMO and VAD technology. Centifugal pumps have been shown to be superior to roller pumps, in terms of reduced haemolysis, neutrophil and complement activation and platelet function [3, 4]. However, a meta-analysis of randomized controlled trials comparing roller and centrifugal pumps in adult cardiac surgery, suggested no significant difference for hematological variables, postoperative blood loss, transfusions, neurological outcomes, or mortality [5]. Both types of pumps are extensively encountered in CPB technology.

Flow generated during CPB, can be pulsatile or non-pulsatile, usually at 2.4 L/min/m^2. Cerebral autoregulation requires a mean arterial pressure of 50–100 mmHg. Clinical and animal studies have compared the two techniques utilizing a variety of clinical end points and microcirculation/perfusion measurements. Pulsatile flow can be provided with roller pumps or centrifugal pumps combined with supported cardiac work or intra-aortic balloon counterpulsation. It has been postulated that pulsatility resembles physiological flow and may offer improved intra- and postoperative microcirculation [6]. Other groups have failed to demonstrate any difference [7].

Monitoring

Adequate tissue perfusion and CPB performance are monitored through a host of devices.

- **Central venous access** is required to monitor central venous pressures, as an indication of adequate preload. Occasionally, Swan-Ganz pulmonary artery or left atrial pressure lines perform this function for the left heart.
- **Arterial lines** (radial, brachial or femoral) ensure continuous systemic blood pressure recording and sampling for arterial blood gases and coagulation function.
- **End tidal carbon dioxide** is monitored via the endotracheal tube, when the patient is ventilated.
- **Temperature probes** (nasal, bladder) are used during cooling, and rewarming of the patient during CPB.
- **Oxygen saturation** is measured peripherally, via dedicated catheters in the arterial line and plethysmography probes. Monitoring of jugular oxygen saturation is of paramount importance during periods of deep hypothermia and circulatory arrest. Monitors of oxygen delivery to the brain include: jugular bulb oximetry, transcranial Doppler sonography, and near infrared spectroscopy (NIRS).
- **Monitoring of cerebral function** is via: quantitative electroencephalography (qEEG) and evoked potential monitoring.
- **Arterial blood gas analysis** for oxygen and carbon dioxide partial pressures can also be used for electrolyte, glucose and lactate monitoring.
- **Transoesophageal echocardiography** is a valuable tool, for ensuring the correct **lines** placement of cannulae, adequate flow during CPB, and inspection of cardiac function and morphology, before and after surgical repair [8].

Temperature and pH Regulation

Modern cardiopulmonary bypass allows the conduct of procedures spanning from normothermia to deep hypothermia. Hypothermia reduces metabolic demand in tissue thus aiding primarily in myocardial and neurological protection. Cerebral metabolism decreases by 6–7% for every 1 °C decrease in temperature from 37 °C. Deep hypothermic arrest takes place at 18–20 °C, and is considered safe between 30 and 60 min of duration.

Deep hypothermic circulatory arrest (DHCA) at 18–20 °C was introduced in order to practice new techniques in congenital and aortic arch surgery [9, 10]. Furthermore DHCA may facilitate non-cardiac procedures that would otherwise be deemed inoperable [11].

Retrograde, followed by antegrade cerebral perfusion were introduced, to minimize neurological complications during periods of circulatory arrest [12–15].

The current trend is to employ combined perfusion techniques; for example, moderate hypothermia with selective antegrade cerebral perfusion (SACP), is associated with a reduction of neurological complications compared to DHCA during arch reconstructions [16].

Tissue perfusion requires the correct supply of oxygenated blood, and an appropriate pH for enzyme function and membrane pore integrity, at given temperatures. During CPB there are two strategies employed in managing pH:

1. **α-stat**: samples are not corrected for temperature, and alkalosis occurs during cooling. Enzyme system function and cerebral auto-regulation adapt to levels adjusted to existing temperature.
2. **pH-stat**: samples are corrected with the addition of CO_2 leading to pH values similar to normal temperatures. Cerebral vasodilatation improves blood flow, especially during periods of cooling, at the expense of a higher risk of debris or gas embolisation [17].

The two strategies produce very little metabolic differences at mild to moderate hypothermia.

Cardioplegia

Cardioplegic solutions can be utilized to arrest the heart, in any of the following combinations:

- Continuous or intermittent,
- Blood or crystalloid,
- Cold (4 °C) or warm (37 °C),
- Antegrade via the aortic root or direct cannulation of the coronary ostia, or retrograde via cannulation of the coronary sinus.

These solutions reduce energy requirements, utilizing high concentrations of potassium 20–40 mEq/L to arrest the cardiac myocyte, in the depolarizing stage of the action potential, and the heart in the diastolic phase of cardiac cycle.

Crystalloid cardioplegic solutions contain a number of substances. Procaine reduces vasoconstriction, magnesium stabilizes the myocardial membrane and preserves ATP, tris-hydroxymethyl aminomethane (THAM) prevents acidosis, and citrate phosphate dextrose (CPD) reduces calcium influx during ischaemic periods.

Blood cardioplegia is a mixture of blood and crystalloid cardioplegic solutions of 4:1 ratio. It helps preserve oncotic pressure, and reduce hemodilution, and contains natural buffers and free radical scavengers. Aspartate and glutamate are also added, to prevent intracellular substrate depletion.

Retrograde cardioplegia, which is delivered via a balloon-tipped catheter to the opening of the coronary sinus in the right atrium, offers the advantage of further myocardial protection in areas of the myocardium distal to severe coronary stenoses, especially in the thicker myocardial territory of the left ventricle, which has higher metabolic requirements. However, the right ventricle has venous drainage proximal to the coronary sinus, and may be compromised, during isolated retrograde cardioplegia administration.

Single shot cardioplegia for induction of cardiac arrest throughout the period of cross-clamping the aorta during cardiac operations, first as the Bretschneider solution containing histidine-tryptophan-ketoglutarate [18], followed by Del Nido cardioplegia containing elements in concentrations similar to the extracellular fluid, mannitol, magnesium sulfate, sodium bicarbonate, potassium chloride and lidocaine [19]. Recent studies have shown it to be equally safe to traditional methods of cardioplegia in coronary and valve surgery [20, 21].

Pathophysiology of Cardiopulmonary Bypass

The CPB circuit is usually primed with up to 1800 ml of crystalloid fluid which, when linked to the patient's circulation leads to a degree of hemodilution. Some hemodilution is desirable during periods of hypothermia, when plasma viscosity increases as does vasoconstriction, a sequence that may impair oxygen delivery. Significant reductions in haematocrit values may lead to organ dysfunction such as acute kidney injury [22]. On occasion, the CPB circuit may be primed with donor blood, especially in cases of chronic anaemia. Other techniques include, retrograde arterial priming, which is employed during CPB [23] and hemofiltration [24], and its subsequent evolution into modified ultrafiltration and zero-balance ultrafiltration [25].

CPB is associated with changes in coagulation and produces inflammatory activation**,** leading to circulatory instability and multi-organ failure [26]. Contact activation of blood elements passing through the tubing, oxygenator and filters of the CPB circuit leads to neutrophil and platelet activation, adhesion and transmigration through tissue endothelium, leading to release of enzymes and free radicals which in turn effect tissue damage [27–29]. Additionally, shear forces and exposure to oxygenators in particular, in combination with centrifugal pumps, can lead to significant haemolysis [30].

Coating strategies aim at improving biocompatibility. Heparin coating has been used for nearly 3 decades. Heparin coating and heparin-polymer coating of the CPB circuit have been associated with reductions in postoperative blood loss and improvements in clinical outcomes [31]. Furthermore heparin-coated circuits may allow conduct of CPB at reduced levels of systemic heparinization with no reported complications [32].

Leukocyte depleting filters remove activated leukocytes from the circulation, in an attempt to reduce the impact of the systemic inflammatory response syndrome. They work by trapping activated and therefore more adherent leukocytes, eliminating a percentage of them, from the circulation. They probably have a role in patients at risk of sepsis or the inflammatory response syndrome.

Miniaturised CPB (Fig. 9.2) is based on the concept of reducing the total surface area of passive elements of the CPB circuit, such as connecting tubing and reservoirs in order to reduce hemodilution and improve biocompatibility, which involves the inflammatory response and coagulation changes [33] Clinical benefits may include decreases in mortality, myocardial infarction and neurological deficits [34]. The application of miniaturized CPB is especially appealing when combined with minimally invasive cardiac operations, such as minimal access aortic valve replacement [35].

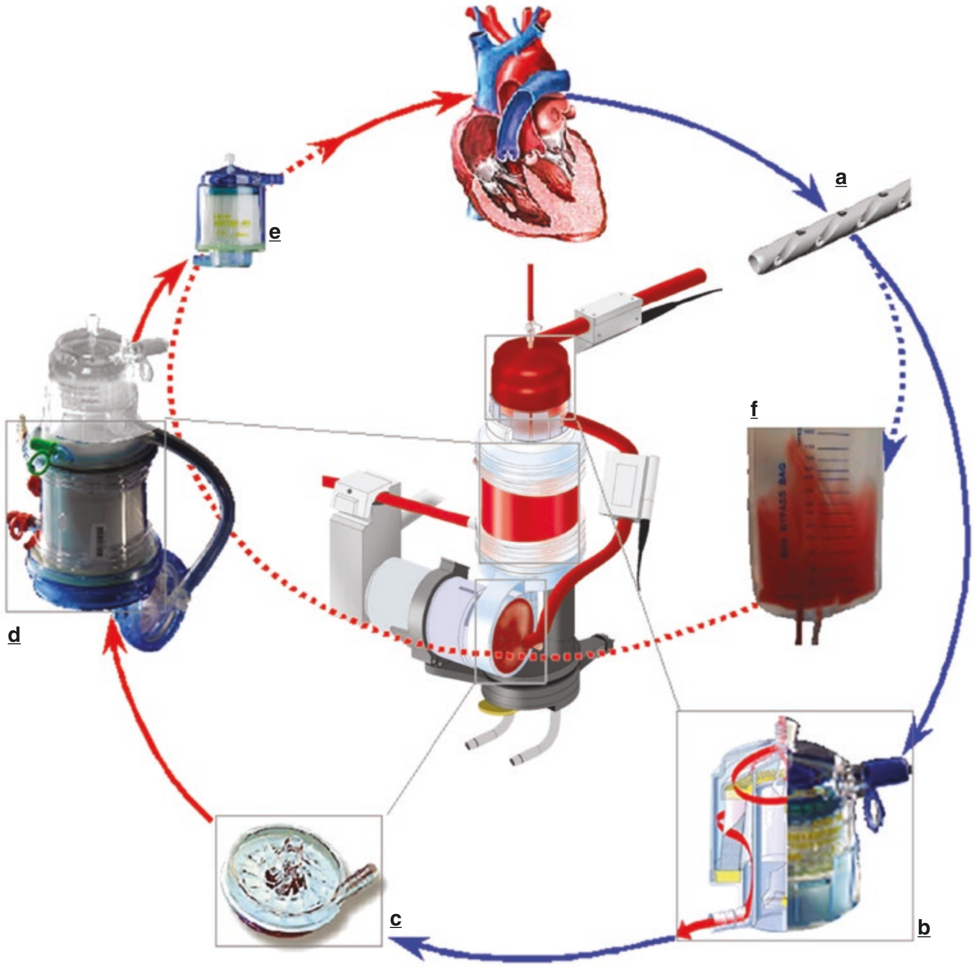

Fig. 9.2 Example of a miniaturised cardiopulmonary bypass circuit configuration. In more detail: (**a**) 29-French OptiFlow venous cannula (Sorin Group, Mirandola, Italy); (**b**) venous air removal device; (**c**) centrifugal pump (Revolution Cardiopulmonary Bypass; Stöckert, Munchen, Germany); (**d**) heat exchange, and oxygenator module (Eos [Sorin Group, Mirandola, Italy]); (**e**) arterial line filter; and (**f**) parallel soft-shell reservoir

Conclusions

In the 2011 update of the Society of Thoracic Surgeons blood conservation clinical practice guidelines minicircuits (reduced priming volume in the minimized CPB circuit) are recognized to reduce hemodilution and are further indicated for blood conservation, especially in patients at high risk for adverse effects of hemodilution (Class I, Level of evidence A indication) [36].

Reductions in blood loss require good preparation in terms of discontinuing where possible, antiplatelet agents and anticoagulants in advance of the operation, timely recognition of coagulation defects developed during CPB, keeping hemodilution to a minimum and maintaining normothermia. In dealing with such defects, the correct type and amount of blood products or other adjuncts such as biological or artificial sealants need to be employed, tailored to the patient's specific circumstances.

CPB technology has evolved, in parallel with developments in both anaesthetic and surgical techniques. This translates in our ability to treat an aging population with more diverse and challenging pathologies, and co-morbidities.

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Myocardial Protection in Adults

10

Francesco Nicolini and Tiziano Gherli

High Yield Facts

- The two pillars of myocardial protection during surgery on cardiopulmonary bypass are hypothermia and electromechanical cardiac arrest.
- In the 1980s, blood-based potassium solutions were advocated to further improve myocardial protection and to reduce myocardial enzymes release.
- Blood cardioplegia and combined antegrade and retrograde delivery is superior to crystalloid cardioplegia and antegrade delivery alone in terms of postoperative morbidity.
- Current techniques of intraoperative myocardial protection are constantly evolving.
- Additional adjuncts such as glutamate/aspartate enhancement, antioxidant supplementation, nitric oxide donors and maintenance of calcium homeostasis seem effective and associated with post-operative improved results.

Introduction

Cardiopulmonary bypass (CPB) is a cornerstone in the history of cardiac surgery because it makes the surgical treatment of most heart diseases possible [1]. CPB is however accompanied by deleterious effects caused by the activation of different pathways such as coagulation and proinflammatory cascades and pathologic oxidative balance [2, 3]. These pathways may explain postoperative dysfunctions in all organs [4] secondary to exposure to CPB. Systemic inflammatory response syndrome (SIRS) in particular remains the most important factor responsible for heart damage after CPB [5].

Despite major advances in technologies and clinical management, and improvements in the strategies for reducing the pro-inflammatory effects of CPB on the myocardium, during cardiac operations the heart suffers. Myocardial deterioration occurs due to organ ischemia caused by aortic cross clamping as well as additional damage secondary to heart reperfusion, or ischemia-reperfusion injury [4]. There is thus continuing debate about the safest and most effective strategy for myocardial protection during cardiac surgery.

Myocardial Injury After Cardiopulmonary Bypass

The exclusion of the heart from the systemic circulation after aortic cross clamping makes the myocardium ischemic, and after the release of aortic clamp and restoration of coronary perfusion post-ischemic myocardial dysfunction is triggered.

Severe hypoxemia during myocardial ischemia produces many deleterious reactions: conversion from aerobic to anaerobic cellular metabolism, high wasting of energy phosphate (i.e., adenosine diphosphate and adenosine triphosphate [ADP, ATP]), intracellular acidosis, and abnormal trans-membrane ionic homeostasis with a pathologic inflow of calcium leading to intracellular calcium ion deposition and phosphate crystals.

Cellular protection derived from the normal activity of free radical scavenging enzymes is lost during myocardial ischemia, and this leads to oxidative stress through the generation of reactive oxygen species (ROS) [6], usually detected in coronary venous blood after aortic clamp release. These radical products or lipid peroxides can cause reperfusion injury and can counteract myocardial recovery [4, 5]. Multifactorial origin is recognized in the pathogenesis of myocardial reperfusion injury [7]. The absence of the protective effect of free radical scavenging enzymes makes the myocardial cell more subject to the damage caused by the burst of free radical formation during reperfusion. Granulocyte-related mechanisms

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are also involved in myocardial reperfusion injury. These include increased neutrophil accumulation and adherence, leading to the release of dangerous proteolytic enzymes, vasoactive substances and free radicals, and culminating in the loss of the structural integrity of the endothelium. Anaerobic ATP production causes greater permeability of cell membrane with massive cellular calcium deposits, and myocardial contracture. Reperfusion may also manifest with the clinical occurrence of arrhythmias, reversible contractile dysfunction (myocardial stunning), and finally with irreversible reperfusion injury with myocardial cell death [8]. The key point in the pathophysiology of reperfusion injury appears to be the extent of damage sustained by the mitochondrion, which is related to the degree of opening of the mitochondrial permeability transition pore (MPTP) [9, 10] at the moment of reperfusion. During reperfusion, re-oxygenation causes a dangerous burst of ROS and the related opening of the MPTP, with a consequent pathologic modification of electrochemical gradients through mitochondrial membranes, and structural disruption of important membrane complexes as proton pumps, ATP synthase, and adenine nucleotide carriers. The degree of damage is proportional to the percentage of MPTP opened. Irreversible myocardial damage and cell necrosis occur when more than 50% of the mitochondria have MPTP open during reperfusion phase (Table 10.1).

Myocardial Protection

Traditionally, the two pillars of myocardial protection during CPB are hypothermia [11] and electromechanical cardiac arrest [12]. Cardioplegia solutions have the dual aim of arresting the heart during diastole and minimizing myocardial energy requirements, in order to obtain an adequate balance between the need for a bloodless, motionless operating field, and the preservation of the myocardial function [13]. Electromechanical arrest has the aim of reducing myocardial metabolism, making it possible for the patient to tolerate intermittent ischemia periods [14, 15]. It is usually achieved with potassium infusion, which leads to diastolic cardiac arrest [13] (Table 10.2).

Table 10.1 Factors contributing to myocardial damage during ischemia/reperfusion

Ischemia	Early reperfusion	Late reperfusion
Hypoxia	Oxygenation	Burst of ROS
		MPTP opening
Depletion of energy stores	Re-energisation	Hypercontracture
Increased intracellular Ca++	Massive Ca++ deposits	Cellular dysfunction
Accumulation of metabolites	Cell membranes swelling	Membrane disruption/ death
Acidosis		
Hyperosmolarity		

Ca++ calcium, *MPTP* mitochondrial permeability transition pore, *ROS* reactive oxygen species

Table 10.2 Principal aims of cardioplegia

• Providing and maintaining electromechanical diastolic arrest of the myocardium
• Feasible cooling of the myocardium
• Containment of myocardial edema and effective buffer capacity
• Limitation of ischemic and reperfusion damage

The solutions are dissolved in crystalloid fluids or in the blood of the patient, and can be delivered intermittently or continuously, using either antegrade (aortic root or coronary ostia), or retrograde (coronary sinus), or both routes of administration.

Hypothermic Methods of Cardioplegic Protection

Hypothermic cardioplegia, introduced in the 1960s, is effective in decreasing myocardial metabolism [16], and in reducing myocardial oxygen consumption [17]. However, electromechanical arrest leads to a 90% reduction in oxygen consumption [13]. Therefore hypothermia offers an additional benefit of about 7% further reduction in oxygen consumption [14, 18].

However, several detrimental effects related to hypothermia have been described [13, 19], particularly the metabolic and functional recovery of the heart due to reduced mitochondrial respiration [20, 21]. In addition, hypothermia appears to adversely impact on the production of myocardial high energy phosphates [22, 23]. Hypothermia also affects several enzymes, such as sodium, potassium, and calcium adenylpyrophosphatase, with consequent modification of the ionic composition of the cell and water homeostasis [13, 20–22]. Other concerns are free radical generation damaging cellular membranes during reperfusion [24], an increase in hemoglobin affinity for oxygen [13, 19, 25], metabolic acidosis, increased plasma viscosity, and lower flow through the micro-capillaries [13]. Hypothermia alone, moreover, does not prevent injury in chronically “energy depleted” (ischemic) hearts.

A retrospective review [26] showed that hypothermic blood cardioplegia is superior to crystalloid based solutions in terms of clinical effects and enzyme release [26]. Hyperkalemic crystalloid cardioplegia is not completely cardioprotective, although it has been shown to be proved effective in causing electromechanical arrest [27]. In fact hematic cardioplegia guarantees better protection because its blood based composition makes its biological properties unique if compared to crystalloid solutions [28].

Normothermic Methods of Cardioplegic Protection

Normothermic myocardial protection is usually performed by the continuous delivery of hyperkalemic normothermic blood during the aortic cross-clamping time [29]. Lichtenstein et al. [30, 31] demonstrate that warm blood cardioplegia offers adequate myocardial protection throughout the cardiac surgery.

The benefits obtained by normothermia include a constant oxygen supply and the preservation of aerobic metabolism, higher oxygen transfer to myocardium, preserved enzymatic activity, normal plasma viscosity [13], low adrenergic response with consequent better cardiac index [32], and decreased CPB-related SIRS [33]. Moreover, low incidence of ventricular arrhythmias after cross-clamp release with the use of warm heart protection has been reported [34]. These benefits appear to be augmented when blood solutions during reperfusion are enriched by the amino acids glutamate and aspartate to replenish key Krebs cycle intermediates depleted by ischemia. These additions improve the reparative processes after a period of myocardial ischemia.

The safe duration of a cardioplegia administration during normothermia is still a matter of debate, and tepid cardioplegia constitutes an alternative method [35, 36]. Similar myocardial oxygen consumption, and less anaerobic lactate and acid washout than normothermic cardioplegia has been reported for this technique [37]. A matter of concern related to normothermia is that it protects the heart, but potentially affects negatively the brain [38]. In fact, neurological complications have been reported more frequently in the normothermic patients. A systemic temperature of 32–33 °C maintained via CPB, combined with tepid blood cardioplegia appears to be more protective for the brain and reduces the risks of neurologic complications [13, 16, 39]. Tepid hematic cardioplegia showed less myocardial injury, better functional myocardial recovery, and demonstrated coronary endothelium integrity [16].

Cardioplegic Solutions

Routes of Administration

All operations include the use of a dedicated pump on the CPB machine for cardioplegic perfusion, specific cannulas for antegrade and retrograde cardioplegia administration and a monitoring-infusion system.

An antegrade cardioplegia cannula is usually placed in the ascending aorta below the site chosen for the aortic cross-clamp (Fig. 10.1). This site can subsequently be used to anastomose the proximal end of a graft during coronary artery bypass grafting (CABG) operation. A 4-0 purse-string polyprolypene suture is used to secure the cannula. When the CPB is running and the heart is empty, thanks to effective systemic venous drainage, the aorta is clamped, and blood antegrade cardioplegia is delivered for 2 min at a rate of 200 mL/min. Sometimes, during CABG, additional antegrade cardioplegia doses can be administered through saphenous vein grafts.

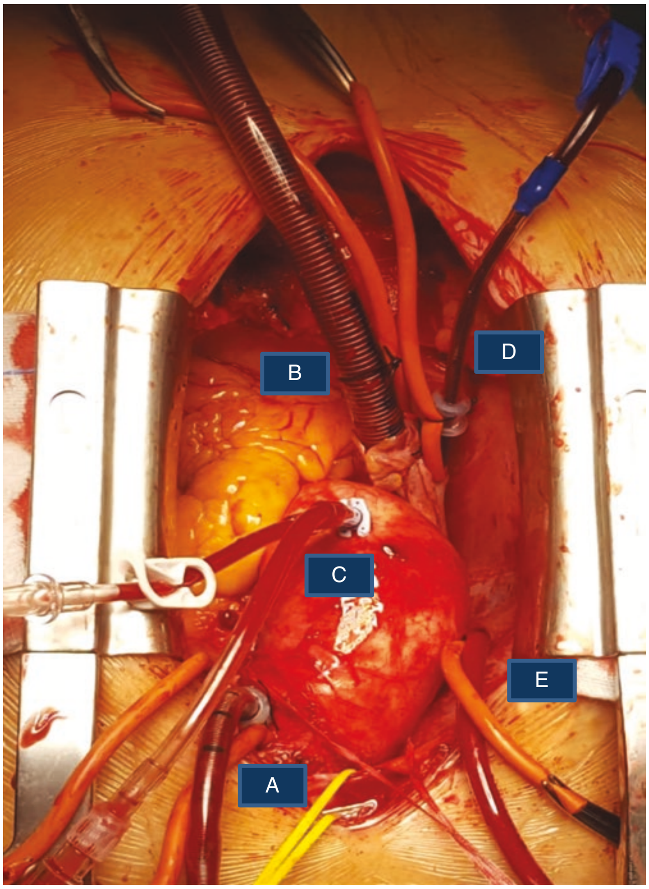

Fig. 10.1 Routes of cardioplegia administration. (**a**) Arterial cannula in ascending aorta; (**b**) Venous cannula in right atrium; (**c**) Antegrade cardioplegia cannula; (**d**) Retrograde cardioplegia cannula; (**e**) Pulmonary vein vent

Retrograde delivery cardioplegia is performed through coronary sinus (Fig. 10.1). Coronary sinus cannulation can be performed before venous cannulation in order to prevent the venous cannula from being an obstacle to the insertion of the retrograde cannula. Otherwise, coronary sinus cannulation can be done on partial bypass with the right atrium slightly distended, with the aim of keeping the sinus ostium open. Transesophageal echocardiography (TOE) guided techniques or surgeon palpation are effective methods to guide the retrograde cannula into correct position. Commercially available retrograde cannulas usually have a malleable stylet and inflatable balloon cannula. The site of introduction on the atrial wall is secured with a 4-0 purse-string polypropylene suture around the cannula. The insertion of the cannula in the sinus should be easy and should make it possible to advance 2–3 cm within the coronary sinus. The correct position is confirmed by TOE images, the presence of dark blood emerging from the cannula, and by the retrograde pressure measuring line showing a "ventricle" like wave on the screen.

In the case of failure to insert the retrograde cannula into the coronary sinus (due to presence of Thebesian fenestrated valve or a narrow orifice), or in the case of surgical procedures requiring right atrium opening, like tricuspid repair/ replacement, transseptal approach to the mitral valve, or MAZE procedures, the right atrium is opened after bicaval cannulation, and retrograde cannula insertion is performed directly into the coronary sinus. Retrograde cardioplegia has proved to be effective in myocardial protection [40]. However, it may not be completely protective for the interventricular septum and the right ventricle [41] due to anatomical variations in the coronary vascular bed [42].

During retrograde infusions, the filling of the posterior descending vein with oxygenated blood is a confirmation of the good perfusion of the venous collateral network. Moreover, the presence of dark blood from the right coronary ostium (observed in the case of aortotomy) or from open coronary arteries incision during CABG means effective and nutritive retrograde blood flow.

Measuring infusion pressure of retrograde cardioplegia delivery prevents edema and endothelial damage and can confirm correct placement of the cannula. The permitted coronary sinus pressure range is from 30 to 40 mmHg at a cardioplegic infusion rate of 200–250 mL/min. If pressure rises over 50 mmHg it may be the result of incorrect positioning of the cannula or heart retraction during circumflex artery grafting which leads to kinking of the venous system. In this case it is mandatory to reduce the flow immediately, and to reposition the cannula, in order to avoid possible injury to the coronary sinus. In this case, a sudden low pressure occurs in the measuring line as a consequence of acute perforation, with the evidence of large amount of red blood within the pericardium. This damage can be repaired with 6-0 prolene sutures or with a pericardial patch. In other circumstances, hematomas may form, but these do not require surgical reparation because low venous pressure allows self-containment of the bleeding after heparin reversal. On the other hand, coronary sinus pressure of <20 mmHg means that the cannula is not inflated or not occluding the coronary sinus. This situation can be solved by palpation and repositioning the cannula tip and balloon.

Cardioplegia Composition and Timing of Delivery

Cardioplegic solutions are usually classified as crystalloid or blood based solutions. The solutions most frequently used in adult cardiac surgery are reported below.

St. Thomas' Hospital solution no 1 (STH-1) is a crystalloid cardioplegic solution with moderately elevated potassium (20 mM) and magnesium (16 mM) and a small additive of procaine (1 mM) in an extracellular ionic matrix that was developed by Hearse and colleagues and introduced clinically by Braimbridge in 1975 [7, 18]. He reported encouraging initial experience in 1977. A comparison of patients undergoing valve replacements using STH-1 and hypothermia (1975–1976) with his previous (1972–1975) practice of coronary perfusion with blood, demonstrated a substantial benefit. The obvious advantages of working in a bloodless field were also acknowledged. Further preclinical studies confirmed the importance of maintaining near to normal extracellular concentrations of calcium and sodium avoiding major fluctuations in these key ions during and following coronary infusion of cardioplegic solutions. Based on the accumulated experience from ex vivo rat and in vivo dog studies an isosmolal *St. Thomas' Hospital solution no 2* (STH-2) was formulated with moderate elevations of potassium (16 mM) and magnesium (16 mM) together with near to normal sodium (120 mM) and calcium (1.2 mM) and a minor content of bicarbonate (10 mM) for initial pH control. This purely ionic and crystalloid solution can, without constraints concerning its administration, be applied for single-dose or multi-dose cardioplegia depending on the duration of aortic occlusion and on the washout by noncoronary collateral blood flow. Commercially available STH-2 (Plegisol™, Hospira Inc., Lake Forest, IL, USA) and STH-1 made up by local hospital pharmacies are still in broad clinical use, mostly for its simplicity of application (Table 10.3).

Custodiol, Histidine-tryptophan-ketoglutarate (HTK), or Bretschneider is an intracellular based crystalloid cardioplegic solution used for myocardial protection in long and complex cardiac surgery and for organ preservation in transplant surgery. It is easily manageable because it is administered as a single dose and has been proved to guarantee myocardial protection for a period of up to three hours [43, 44] without interruption. HTK was first proposed by Bretschneider in the 1970s [45]. It is an intracellular, crystalloid cardioplegia characterized by low sodium and calcium content. The mechanism of action is based on sodium depletion of the

Table 10.3 Composition of the St. Thomas' Hospital cardioplegic solutions

Component (mM)	STH-1	STH-2
Sodium chloride	144	120
Sodium bicarbonate		10
Potassium chloride	20	16
Magnesium chloride	16	16
Calcium chloride	2.2	1.2
Procaine hydrochloride	1	
pH	5.5–7.0	7.8
Osmolality (mOsm/Kg H_2O)	300–320	285–300

Table 10.4 Composition of Custodiol™ cardioplegia solution

Ingredient	Value
Na+	15 mmol/L
K+	9 mmol/L
Mg2+	4 mmol/L
Ca2+	0.015 mmol/L
Histidine	198 mmol/L
Tryptophan	2 mmol/L
Ketoglutarate	1 mmol/L
Mannitol	30 mmol/L
pH	7.02–1.20

Table 10.5 Methods of cold cardioplegia perfusion

Induction	Antegrade delivery	Retrograde delivery
Cold	300 mL/min × 2 min	150 mL/min × 2.5 min
Maintenance	200 mL/min × 1 min	200 mL/min × 1 min
Reperfusion	150 mL/min × 2 min	150 mL/min × 2 min

Table 10.6 Composition of cold blood cardioplegia solution

Ingredient	Concentration delivered (mixture 4:1 ratio with blood)
Potassium chloride	20 mmol/L
Magnesium chloride	17 mmol/L
Calcium chloride	2 mmol/L
Procaine hydrochloride	1 mmol/L
Sodium bicarbonate	25 mmol/L
pH	7.35–7.45
Osmolality	280–300 mOsm

extracellular space, which causes a hyperpolarization of the myocyte membrane, inducing cardiac arrest in diastole. The components of Custodiol are listed in Table 10.4.

Cold blood cardioplegia is a method which appears to combine the advantages of hypothermia and blood solutions, and appears to complete myocardial recovery after long periods of ischemia in normal hearts. Blood cardioplegia consists of four parts of blood to one part of crystalloid solution. This limits the hemodilution occurring with crystalloid cardioplegia during repeated infusions. Table 10.5 summarizes flow rates usually employed in normal hearts. In the case of hypertrophied hearts, flow rates are increased by 50–100 mL/min. High-dose potassium (20–30 mEq/L) allows heart arrest during both warm and cold induction (Table 10.6). Some authors recommend enrichment with amino acids (glutamate/aspartate) in high-risk patients such as those affected by depressed left ventricular function, ongoing ischemia, or hypertrophy [46, 47]. Maintenance doses during cold cardioplegic infusion are based on low dose potassium solutions. At the end of surgical procedures, patients receive a terminal warm perfusate (“hot shot”). This solution is usually blood based and substrate enhanced, with no potassium, and is recommended in patients with poor ventricular function or after long cross-clamp times in complex surgical procedures.

Table 10.7 Delivery protocol for warm blood intermittent cardioplegia

Flow rate				
Dose	Roller pump (mL/min)	Syringe pump (mL/h)	Duration (min)	[K+] (mEq/L)
First	300	(Push 2 mL then 150)	2	18–20
Second	200	120	2	20
Third	200	90	2	15
Fourth	200	60	3	10
Fifth	200	40	4	6.3
Sixth	200	40	5	6.3

Table 10.8 Composition of Fremes’ solution

Ingredient	Value
Dextrose 5% water	500 mL
Potassium chloride	50 mEq
Magnesium sulphate	9 mEq
Tromethamine	6 mEq
CDP solution	10 mEq
Osmolality	425 mOsm/L
pH	7.95
Total volume	557 mL00 4

Intermittent warm blood cardioplegia, first described by Calafiore et al., is based on intermittent doses of patient blood with potassium added. After the first dose (600 mL in 2 min), additional doses are given after construction of each distal CABG anastomosis or after 15 min. This proved to be a safe, reliable, and effective technique of myocardial protection, particularly in CABG procedures [48]. Delivery protocol is shown in Table 10.7.

Adding retrograde perfusion to warm blood antegrade cardioplegia improves subendocardial perfusion, avoids direct ostial cannulation during aortic valve procedures, limits repositioning of retractors during mitral procedures, eliminates all the concerns related to the distribution of cardioplegia due to severe coronary artery stenosis and allows flushing of air bubbles and atheroma debris during coronary reoperations. Switching from antegrade to retrograde perfusion increases oxygen uptake and lactate washout, confirming that each strategy perfuses different areas. Therefore, both antegrade and retrograde perfusions are often required (Fig. 10.1), at least intermittently.

Continuous cardioplegic perfusion has been advocated by Salerno et al. to avoid ischemia caused by intermittent antegrade or retrograde delivery [49–51]. The heart is arrested using high-potassium blood cardioplegia, containing four portions of blood to one portion of high-potassium Fremes’ solution (Table 10.8). After the diastolic arrest, the perfusion system is switched to the retrograde flow. Low-potassium Fremes’ solution (same composition as high-potassium Fremes’ solution but KCI = 30 mEq/L) is administered in the same proportion of components at a maximum mean pres-

Table 10.9 Adjuncts in cardioplegia solutions

Adjunct	Advantages	Disadvantages	References
Calcium- blockers	• Preservation of high-energy phosphates • Improved myocardial metabolism • Reduced ischaemic injury	• Potent negative inotrope effect • Need for atrioventricular sequential pacing	[52]
Magnesium	• Marginal reduction in the incidence of new-onset postoperative atrial fibrillation	• No advantages in terms of low cardiac output, inotropic utilization, myocardial infarction, length of ICU stay, and in-hospital mortality	[53]
Beta-blockers (esmolol)	• To prevent or treat arrhythmias and myocardial ischemia • To test the reversibility of systolic anterior motion in cardiac surgery	• Negative inotropic and chronotropic effects • Low atrioventricular conduction and cardiac block	[54]
Local anesthetics (lidocaine, procaine)	• Membrane stabilization • Spontaneuos return to sinus rhythm after surgery	• Hypersensitivity • Depression of contractile funciton	[55]
Halogenated anesthetics (propofol, sevoflurane)	• To decrease perioperative myocardial damage with a mechanism directly related to pre-conditioning and post-conditioning.	• Better understanding of mechanisms of action and benefits is mandatory	[56]
Nitric oxide (NO) donors (L-arginine)	• NO donors reduce myocardial injury and the inflammatory response • NO donors prevent the apoptosis of cardiomyocytes • NO synthesis • L-arginine infusion reduces levels of markers of myocardial damage	• Further studies needed to finally validate this approach	[57–59]
Ischemic preconditioning	• Postoperative improvement of cardiac index • Reduced inotropic support • Antiarrthythmic effects	• Doubts about enhancement of cardiac protection	[60–62]

sure of 40 mm Hg, measured in the coronary sinus cannula. Retrograde cardioplegic delivery should not exceed 250 mL/min. The infusion pressure and flows are constantly monitored. In the case of persistent electrical activity, additional high-potassium cardioplegia (usually 200–300 mL of high-potassium Fremes' solution) can be delivered retrogradely or, otherwise, the surgeon can administer higher maintenance potassium concentration (40 mEq/L).

Numerous adjuncts in cardioplegia solutions have been evaluated or are currently under investigation. They are summarized in Table 10.9.

Conclusion

Since the beginning of cardiac surgery in the early 1950s, effective protection of the heart has been a mandatory step to counteract the risks and potential damage derived from myocardial ischaemia occurring during cardiac operations. Daily surgical practice is based on a consensus method with the use of hyperkalaemic cardioplegic solutions that allow satisfactory myocardial protection. This technique induces a cellular depolarized arrest and remains the cornerstone of cardiac protection regardless of chemical composition (crystalloid or blood solutions), temperature (hypothermic or warm solutions), or presence or absence of various additives. However it is widely acknowledged that the characteristics of cardiac surgery patients have changed considerably. Nowadays, patients are older and sicker, and present for surgery more frequently with a history of heart failure or acute coronary syndrome. New concepts in myocardial protection may bring various improvements. The new strategies however require further examination and investigation in order to respond to the new challenges that high-risk patients pose.

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11

Heparin-Induced Thrombocytopenia

Benilde Cosmi

High Yield Facts

- Anticoagulation with unfractionated heparin is the mainstay for extracorporeal circulation and cardiac surgery.
- Heparin use can be complicated by a rare immuno-mediated adverse reaction (HIT-heparin induced thrombocytopenia) which is due to the development of IgG antibodies against complexes of heparin bound to a product of platelet activation, that is platelet factor 4 (PF4). The immune complexes of IgG with heparin/PF4 can activate platelets, with thrombocytopenia, due to intravascular platelet consumption, and paradoxical thrombotic complications, due to coagulation activation.
- HIT frequency in cardiac surgery is estimated to be around 1–3%.
- HIT diagnosis requires an assessment of a typical clinical picture (thrombocytopenia after heparin exposure, with thrombosis-HITT or without thrombosis-isolated HIT) with the determination of pre-test probability with a clinical prediction rule, such as the 4Ts score, and the detection of platelet activating antibodies.
- Immunological assays such as ELISAs and PaGIAs are used as screening assays as they have a high negative predictive value, but poor specificity with the risk of false positives and of overdiagnosis.
- Functional tests, such as serotonin release assay and heparin induced platelet aggregation, can reliably detect platelet activating antibodies but they are available only in specialized laboratories.
- HIT diagnosis can be excluded by a negative immunological assay of high sensitivity.
- HIT treatment requires discontinuing heparin in any form and the administration of alternative non-heparin anticoagulants to counteract coagulation activation and treat thrombotic complications.
- Argatroban and danaparoid are currently the only non-heparin anticoagulants licensed for HIT. Bivalirudin is an option in cardiac surgery for HIT patients.
- There is no reversal agent equivalent to protamine for any of the non-heparin alternative anticoagulants.
- For HIT patients who require urgent cardiac surgery, use of plasmapheresis, bivalirudin, or antiplatelet agents such as tirofiban, iloprost with UFH may be considered, albeit with increased risks of bleeding.

Introduction

The anticoagulant effect of heparin, especially unfractionated heparin (UFH), is a mainstay for extracorporeal circulation including extracorporeal membrane oxygenation, left heart bypass, hemofiltration, hemoperfusion, and cardiopulmonary bypass (CPB) and also in cardiovascular surgical procedures including off-pump coronary artery bypass graft surgery. Heparin is widely available, can be easily monitored and its anticoagulant effect can be rapidly and safely reversed by protamine. However, heparin use can be associated with a potentially lethal, although rare, complication called heparin-induced thrombocytopenia (HIT).

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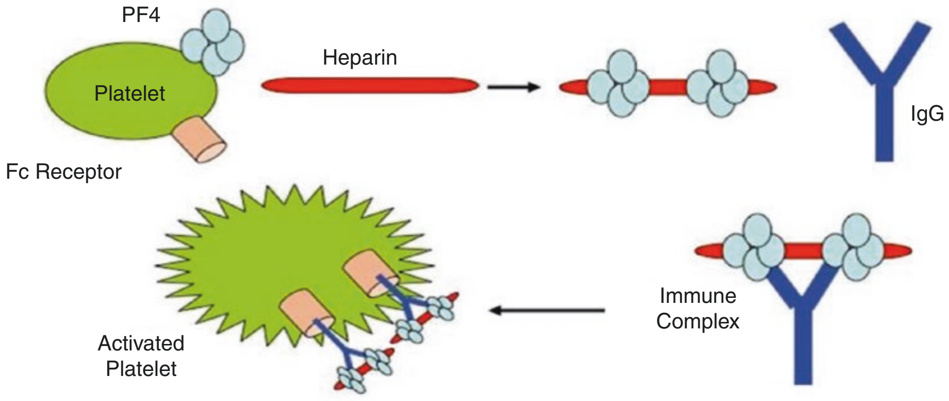

Fig. 11.1 Pathophysiology of heparin-induced thrombocytopenia (*PF4* platelet factor 4, *IgG* immunoglobulin G)

HIT is an adverse drug reaction due to the binding of heparin to endogenous platelet factor 4 (PF4) or other polyanions, which can elicit an immune response with the development of IgG antibodies against the complex of PF4 and heparin or other polyanions. IgG antibodies bound to PF4-heparin complexes can cross-link the platelet surface Fcγ receptor IIa (FcγRIIa). Platelets are thus activated with intravascular aggregation, consumption and thrombocytopenia, which is not associated with bleeding, but with a paradoxical prothrombotic state (Fig. 11.1). Venous and/or arterial thrombosis [1] may ensue simultaneously in several vascular beds, with a catastrophic thrombotic syndrome [2].

HIT is a clinico-pathological syndrome defined by: (1) one or more clinical events, primarily thrombocytopenia without (isolated HIT) or with thrombosis (HITT—HIT Thrombosis); and (2) detection of a heparin-dependent and platelet activating immunoglobulin (usually IgG) using a sensitive and specific laboratory assay [3].

Pathogenesis

Although HIT was first described in 1958 [4] and detailed in 1973 [5], its pathogenesis is still a matter of scrutiny [6]. HIT immune response is atypical as IgG antibodies are generated rapidly (detectability, median day 4) and without IgM class precedence, suggesting a secondary immune reaction [1, 6]. PF4 is a chemokine [7] which is synthetized by megakaryocytes, stored in and released from α-granules upon platelet activation. PF4 is a highly positively charged tetrameric molecule with a high affinity for large, anionic molecules such as heparin. Optimal complex formation can occur at high PF4 levels and prophylactic dose UFH, while therapeutic-dose low molecular weight heparin (LMWH) concentrations are too high for optimal complex formation and concentrations of fondaparinux are usually below the optimal stoichiometric range [8]. For a given degree of PF4 availability, complexes formation occurs with decreasing frequency with: prophylactic dose UFH > therapeutic dose UFH > prophylactic dose LMWH > therapeutic dose LMWH > fondaparinux [9]. PF4 binding to heparin entails a conformational change with exposure of the neoepitope necessary for antibody binding [10]. Immunization occurs more frequently after strong rather than minor platelet activation such as in surgical, rather than medical patients.

The pathogenic immunoglobulin is an IgG, while heparin/ PF4-reactive IgM and IgA antibodies are also formed, but their role in HIT is uncertain [2]. Complexes of heparin/ PF4 and IgG bind to platelets via the platelet surface receptor FcRγIIa [2]. IgG immune complexes produce receptor cross-linking, which strongly activates platelets with intravascular platelet aggregation, with thrombocytopenia and thrombosis due to enhanced thrombin generation [11]. As a result, HIT can be complicated by both venous and arterial thrombosis and the degree of thrombocytopenia reflects the magnitude of platelet activation.

Timing

The timing of HIT clinico-pathological manifestations is related to the immunological basis of this adverse event (Table 11.1). A specific sequence of events is present in the majority of cases (60%) (typical onset HIT): heparin exposure (day 0), IgG antibody generation (day 4) followed by the onset of the platelet count fall (median, day 6) followed by a >50% fall (median, day 8) followed by thrombosis (median, day 10) [2]. Thrombocytopenia (defined as a platelet count $<150 \times 10^9$/L) occurs in 85–90% of cases, but if a proportional fall in the platelet count (e.g., 30–50% fall even if the nadir remains $>150 \times 10^9$/L) is considered, this increases to 90–95% of cases [12].

Table 11.1 Classification of heparin-induced thrombocytopenia

Feature	Type I	Type II
Frequency	10–20%	1–3%
Nadir platelets/mm^3	1,00,000	50,000
Timing of onset	1–3 days	5–10 days
Antibody mediated	None	HIT antibody (IgG-HeparinPF4)
Bleeding	Nil	Rare
Thrombosis	Nil	30–50%
Treatment	Nil	Stop heparin and use nonheparin anticoagulants
Danger to life	None	Serious complications endanger life

Clinical Picture

Any vascular bed, especially at sites of vascular injury, can be affected by thromboembolic complications. In medical and orthopedic patients, venous thromboses are the majority, whereas in cardiac or vascular surgery patients, arterial and venous thromboses occur at a similar frequency. Limb ischemia may result in amputation in 5–10% of patients with HIT. The mortality rate is high (8–20%), regardless of therapy [13]. Rare complications include skin necrosis, thromboses at unusual sites, such as the adrenal veins with adrenal hemorrhagic necrosis or cerebral venous sinuses, disseminated intravascular coagulation with depletion of fibrinogen [14] or post-intravenous heparin bolus anaphylactoid reactions. In case of re-exposure to heparin within 1 (rarely up to 3) months, HIT can occur by day 1 (rapid onset HIT; 30% of cases) from the persistence of heparin-dependent antibodies [6]. HIT can rarely have a delayed onset from several days to a few weeks after heparin exposure, due to persisting high titers of heparin-dependent antibodies [15]. Following an episode of HIT, the antibodies can become non-detectable within days or a few weeks (<100 days) [1], including even when heparin is continued. Although HIT recurrence cannot be excluded, re-exposure to heparin may be uneventful in such patients for the lack of an early anamnestic response, allowing for deliberate short time re-use in situations such as cardiac or vascular surgery [1, 7].

Frequency

HIT frequency varies in different populations (Table 11.2). After cardiac surgery only 1–3% of patients with HIT-IgG develop clinical HIT, in spite of a prevalence of anti-heparin/PF4 antibodies up to 50–75% at 10 days with platelet counts lower than 100 × 10^9/l in up to ≈40% of post-cardiac surgery patients [16–18]. Reasons for such an "iceberg" model [3] in which many patients are antibody positive and only a minority develops HIT are unclear. As a result, thrombocytopenia and coincidental detection of anti-heparin/PF4 antibodies after cardiac surgery can be frequent, although antibodies are not platelet activating and therefore not causing thrombocytopenia. HIT diagnosis in such patients is particularly challenging and a relevant safety issue [18].

Table 11.2 Frequency of HIT in different patient populations

Surgical	1–5% if exposed to UFH 0.1–1% if exposed to UFH flushes or to LMWH
Medical	1% in cancer patients 0.1–1% with UFH 0.6% with LMWH 0.4% in intensive care units patients
Pediatric	0.058% HIT 0.046% HIT with thrombosis in patients on UFH
Pregnancy	<0.1%
Hemodialysis	0.8–3%
Women	1.5- to 2-fold higher risk than men

LMWH low molecular weight heparin, *UFH* unfractionated heparin

Diagnosis

A typical platelet count decrease during heparin exposure should prompt appropriate clinical assessment and laboratory detection of platelet activating antibodies [12]. Serial platelet counts have the highest benefit in those patient populations at risk of HIT >1% such as surgical or trauma patients [12]. A baseline platelet count before heparin is recommended by most guidelines. The recommended frequency of platelet counts after heparin exposure varies, according to the type of patient as shown in Table 11.3. Platelet count usually falls by approximately 38% immediately after CPB (and continues to decline for the first 1–2 postoperative days before rising again in a continuous fashion to a level above the preoperative levels), therefore a fall in platelet count that begins >4 days postoperatively (day of surgery = day 0), and thrombocytopenia that persists for >4 days after surgery should be suspicious for HIT development [12]. Surgery is a strong immunogenic risk factor for HIT and therefore it is recommended that the day that heparin is restarted after surgery is considered day 0 of heparin use, even if heparin was administered preoperatively. Similarly, if heparin is used during surgery, the date of surgery becomes day 0 [18].

Clinical assessment for HIT should be carried out with clinical prediction rules (CPR) to determine pretest probability (PTP) which has three purposes: (1) to establish whether to start treatment in case of high PTP (the rate of thrombosis is approximately 5% per day without treatment) while waiting for laboratory test results; (2) to establish the need of confirmatory laboratory testing for anti-heparin/PF4 antibodies; (3) to interpret laboratory results as isolated HIT antibodies are both frequent and not diagnostic [12].

Table 11.3 Timing of serial platelet counts to screen for HIT

	Baseline platelet count before heparin	Frequency after heparin exposure
British Committee for Standards in Hematology (BCSH) [19]	Yes (level of evidence 2C)	Post-operative patients and cardiopulmonary bypass patients who have been exposed to heparin in the previous 100 days and are receiving any type of heparin should have a platelet count determined 24 h after starting heparin (level of evidence 2C)
American College of Chest Physicians (ACCP ninth edition) [12]	–	Every 2 or 3 days from day 4 to day 14 (or until heparin is stopped, whichever occurs first) (level of evidence 2C)

Table 11.5 HIT scoring system after cardiopulmonary bypass (CPB)

Category	Clinical scenario	Points
Platelet count	Pattern A (platelet count begins torecover after CPB but then beginsto fall again >4 days after CPB)	2
	Pattern B (thrombocytopenia occurs immediately after CPB and persists for >4 days without recovery)	1
Time from CPB to index date	≥5 days	2
	<5 days	0
CPB duration	≥118 min	1
	<118 min	0

Total score: ≥2 points = high probability of HIT; total score: <2 points = low probability of HIT
From [23]

Table 11.4 4Ts score clinical prediction rule for heparin-induced thrombocytopenia (HIT) diagnosis

Category	2 points	1 point	0 point
Thrombocytopenia	Platelet count fall >50% AND platelet nadir 20 × 10^9/L	Platelet count fall 30% 50% OR platelet nadir 10–19 × 10^9/L	Platelet count fall <30% OR platelet nadir <10 × 10^9/L
Timing of platelet count fall	Clear onset between days 5 and 10 OR platelet fall 1 day (prior heparin exposure within 30 days)	Consistent with days 5 and 10 fall, but not clear (e.g. missing platelet counts) OR onset after day 10 OR fall ≤1 day (prior heparin exposure 30–100 days ago)	Platelet count fall <4 days without recent heparin exposure
Thrombosis or other sequelae	New thrombosis (confirmed) OR skin necrosis at heparin injection sites OR acute systemic reaction after intravenous heparin bolus	Progressive or recurrent thrombosis or non-necrotizing (erythematous) skin lesions or suspectedthrombosis (not proven)	None
Other causes for thrombocytopenia	None apparent	Possible	Definite

Low probability score (≤3): a high negative predictive value for HIT (99.8%)
Intermediate (4–5): positive predictive value of 14%
High (>6) probability scores: positive predictive value 64%
From [22]
Guidelines of BCSH recommend that HIT can be excluded by a low pre-test probability score without the need for laboratory investigation (level of evidence 2B) while if the pre-test probability of HIT is not low, heparin should be stopped and an alternative anticoagulant started in full dosage whilst laboratory tests are performed (level of evidence 1C) [19]

The most widely evaluated CPR for HIT is the 4Ts score (Thrombocytopenia, Timing, Thrombosis, and oTher causes for thrombocytopenia) [20, 21] (Table 11.4) which is more useful to exclude HIT if low, while if it is intermediate or high, laboratory testing is warranted. A clinical prediction rule has also been proposed for HIT after cardiopulmonary bypass [23] (Table 11.5) but it requires validation in large prospective studies before it can be recommended for clinical use [24].

Two types of laboratory tests are available: (1) immunological and (2) functional. Platelet activating antibodies are only detected by functional assays, such as the ^{14}C serotonin release assay (SRA) and heparin induced platelet activation (HIPA), which are generally accepted as the reference standard. However, such tests are complex, not commercially available and require referral to specialized reference laboratories [25].

Non specialized laboratories can perform immunological assays which are commercially available, such as enzyme-linked immunosorbent assays (ELISAs) and particle-based immunoassays. They can detect anti-heparin/PF4 antibodies regardless of their ability to activate platelets and can be polyspecific or IgG specific.

The majority of clinical laboratories employ commercially available ELISAs whose major drawback is the potential for false positive results with HIT overdiagnosis as non-pathogenic antibodies are detected. ELISAs that only detect IgG antibodies appear to have better specificity for HIT (IgM and IgA antibodies are unlikely to cause HIT) [12]. Table 11.6 shows the characteristics of immunological assays for HIT. Guidelines agree that HIT can be excluded in patients with an intermediate pre-test score who have a negative

Table 11.6 Laboratory immunological assays for HIT

	Antibodies specificity	Measurement scale	Practical issues	Guidelines recommendations
Enzyme-linked immunosorbent assay (ELISA)	Polyspecific IgG specific	Optical density (OD): Low threshold: below or equal to OD 0.7; Intermediate threshold: between OD 0.8 and 1.4; High threshold: above OD 1.4	Requires specialised laboratory, determination in batches, daily determination rarely possible	Very sensitive with negative predictive value is high; positive predictive value is low with high rate of false positives and low specificity The combination of a threshold >1.0 OD with a high clinical suspicion for HIT (e.g. intermediate or high 4T's score) may have a similar accuracy for diagnosing HIT as the reference standard [12]
Particle gel immunoassay (PaGIA)	Polyspecific	Visual assessment of agglutination; Quantification using titration studies; positive/negative	Determination in standard laboratories possible, 24-h service, observer-dependent	A low or intermediate 4Ts score plus negative PaGIA excludes HIT
Chemiluminescent immunoassay	Polyspecific	Detection of emitted light; Low threshold: below 1.0 U/ml; intermediate threshold: between 1.0 and 2.8 U/ml; high threshold: above 2.8 U/ml	Automated determination possible, 24-h service, expensive	

The Guidelines of the BCSH [19] recommend that non-expert laboratories should use an antigen assay of high sensitivity for measuring only the IgG class, and report the actual optical density, degree of inhibition by high dose heparin, and the cut-off point for a positive test, rather than simply reporting the test as positive or negative (level of evidence 1B). In making a diagnosis of HIT, the clinician's estimate of the pre-test probability of HIT, together with the type of assay used and its quantitative result (ELISA only) and information on reversal using higher doses of heparin should be used to determine the post-test probability of HIT (level of evidence 2B)

particle gel immunoassay (level of evidence 2B). HIT can be excluded in all patients by a negative antigen assay of high sensitivity (level of evidence 1A) [12].

Treatment

When HIT is diagnosed, heparin in any form must be immediately withdrawn (heparin flushes and heparin coated catheters as well) and new or recurrent thrombotic events should be looked for with the appropriate objective tests, such as compression ultrasound of the lower limbs. However, stopping heparin or substitution with vitamin K antagonists (VKAs) is insufficient to inhibit thrombin generated by HIT, as further thrombotic events can occur in untreated HIT in 30–75% of cases with 5–10% mortality [12]. Non cross-reactive non-heparin anticoagulants should be initiated, regardless of the presence of thrombosis at the time of HIT diagnosis. LMWH cross-reacts in-vivo in approximately 50% of cases. Alternative anticoagulants have been evaluated for HIT on the basis of their in-vitro and ex-vivo lack of cross reactivity with heparins, such as argatroban and bivalirudin, while danaparoid demonstrates cross reactivity in-vitro which is only rarely evidenced in-vivo [26]. Fondaparinux is highly immunogenic. However, it is unlikely to form complexes large enough to cause platelet activation [27]. Warfarin, especially when used in isolation, can increase the risk of microvascular thrombosis in HIT and it should be started only after a substantial resolution of platelet activation, and thus of the thrombocytopenia, with platelets >150 × 10^9 L at a stable plateau for 2 consecutive days [7] and after a minimum overlap of 5 days between non-heparin anticoagulants and VKAs. Argatroban also prolongs the prothrombin time and this should be taken into account when starting VKA. Patients on argatroban undergoing transition to warfarin should have an INR >4 for 2 days prior to discontinuing argatroban (level of evidence 2C) [19].

The best non-heparin anticoagulant for HIT is uncertain, as no head to head comparisons have been conducted. Dosing and availability of alternative anticoagulants in HIT are shown in Table 11.7. Guidelines agree that platelets should not be given in HIT, but they may be given in case of bleeding.

The BCSH guidelines recommend that patients should be therapeutically anticoagulated for 3 months after HIT with a thrombotic complication (level of evidence 1A) and for 4 weeks following HIT without a thrombotic complication (level of evidence 2C) as HIT can be considered a transient removable risk factor [19].

Table 11.7 Alternative non-heparin anticoagulants in heparin-induced thrombocytopenia (HIT)

Non-heparin alternative anticoagulants	In-vitro and in vivo heparin cross reactivity	(a) Route of administration (b) Half-life	(c) Route of elimination (d) Antidote	Countries in which drugs are approved for HIT	(g) Dosage in HIT (h) Monitoring (j) Bleeding rate
Argatroban: synthetic direct thrombin inhibitor derived from the amino acid L-arginine, it binds reversibly and inhibits thrombin catalytic active site, it has an immediate onset of action	Absent	(a) IV (b) 45 min	(c) Hepatic (d) No Hemodialysis, Hemoperfusion	USA (also approved for PCI in HIT or HITT), Canada, Australia, Europe (Austria, Denmark, France, Germany, Iceland, Italy, Netherlands, Norway, UK, Spain, Sweden)	(g) 2 μg/kg/min (max 10 μg) (h) APTT ratio 1.5–3.0 APTT repeated within 4 h of any dose adjustment and at least once daily (j) 6–7% (g) 0.5–1.2 μg/kg/min in liver disease or critical illness or after cardiac surgery (h) APTT ratio 1.5–3.0 APTT repeated within 4 h of any dose adjustment and at least once daily (g) 350 μg/kg bolus in patients with HIT undergoing PCI (h) ACT between 330 and 450 s For ACT 300–450 s, initial dosage 25 μg/kg/min if ACT <300 s, dosage adjustment to 40 μg/kg/min if ACT >450 s, dosage adjustment to 15 μg/kg/min
Danaparoid: heparinoid composed of a mixture of heparan sulphate, dermatan sulphate and chondroitin sulphate with both antithrombin mediated anti-Xa and anti-IIa activity	Cross-reactivity with PF4/heparin antibodies in 3.2% of patients	(a) IV (b) 24 h	(c) Renal (d) No	Europe, UK, Australia	(g) Intravenous bolus (1500 U if patient <60 kg; 2250 U if 60 to <75 kg; 3000 U if 75–90 kg; 3750 U if >90 kg) followed by IV infusion of 400 U per hour for 4 h, 300 U per hour for 4 h, then 150–200 U per hour (h) Adjust to anti-Xa activity of 0.5–0.8 U/ml (with use of danaparoid standard curve) (j) 8.1%
Bivalirudin: hirudin analogue, binding both the active and fibrin-binding sites of circulating and clot-bound thrombin	Absent	(a) IV (b) 25 min	(c) Renal + enzymatic degradation (d) No hemodialysis	USA and Canada for PCI in HIT or HITT (available in Europe for PCI in AMI)	(g) IV bolus of 0.75 mg/kg followed by 1.75 mg/kg/h during procedure and max 4 h, afterwards 0.2 mg/kg/h up to 20 h reduction of the rate of infusion to 1 mg/kg/h for CrCL <30 ml/min or 0.25 mg/kg/h if on dialysis (h) ACT >300 s 5 min after bolus dose (j) 2.4% in PCI
Fondaparinux: anti-Xa synthetic pentasaccharide	Not in-vivo	(a) Subcutaneous (b) 17–20 h	(c) Renal (d) No	None	(g) 5.0 mg subcutaneously once daily for patients <50 kg; 7.5 mg for 50–100 kg; 10.0 mg for >100 kg (h) No

IV intravenous, *PCI* percutaneous coronary interventions, *APTT* activated partial thromboplastin time, *ACT* activated clotting time, *AMI* acute myocardial infarction, *CRCL* creatinine clearance

Management of HIT in Cardiac Surgery

In case of acute (when there is still thrombocytopenia) or subacute HIT (that is recent HIT with platelet count recovery but persisting HIT antibodies) or a history of HIT, guidelines suggest delaying surgery (if possible) until HIT has resolved and HIT antibodies are negative (level of evidence 2C) [12, 19] and recommend intra-operative UFH in preference to other anticoagulants, which are less validated for this purpose. There are also data indicating that UFH can be safely used in patients with previous HIT because HIT antibodies are transient, that there is no anamnestic immune response in HIT, there is an association with recent heparin exposure (previous 100 days) but not with more remote heparin exposure [12]. UFH is suitable in these patients only during CPB, ensuring pre- and post-surgery non-heparin anticoagulation [12, 28, 29].

In patients requiring urgent cardiac surgery, alternative strategies include: bivalirudin; the combined use of platelet inhibitors (i.e. epoprostenol, iloprost, or tirofiban) with UFH; and plasma exchange to permit UFH on CPB [12]. Argatroban and danaparoid cannot be recommended for CPB [12, 16, 18]. No reversal agents are available for non-heparin alternative anticoagulants.

Bivalirudin in Cardiac Surgery

Guidelines favour the use of bivalirudin for HIT where cardiac surgery is urgent and cannot be postponed [12, 19]. Appropriate bivalirudin dosing has been established with monitoring by a validated activated clotting time (ACT) measurement (Table 11.8), based on studies assessing bivalirudin in off-pump and on-pump cardiac surgery [30]. Special surgical and perfusion considerations should be undertaken to avoid blood stagnation in the extracorporeal circuit and the operative site, as bivalirudin is cleaved by thrombin in stagnant blood [31]. Only bivalirudin has been used successfully in off-pump coronary artery bypass grafting (Table 11.9) [18].

Table 11.8 Protocol for bivalirudin use in cardiopulmonary bypass (CPB)

General guidelines
All flush solutions, lines, and cell saver must be prepared with bivalirudin (0.1 mg/ml; 1 ml for every 5 ml cell saver processed) instead of heparin
Bivalirudin is supplied as 250 mg/vial and is typically prepared as 250 mg in 50 ml (although 500 mg in 100 ml is probably more convenient)
Bivalirudin dosing and monitoring before CPB
Initial iv bivalirudin bolus: 1.0 mg/kg body weight and initiate continuous iv infusion: 2.5 mg/kg/h
Bivalirudin added to pump circuit volume: 50 mg
Monitoring by ACT: A prolongation of ≥2.5-fold of baseline ACT level indicates adequate anticoagulation with bivalirudin
Bivalirudin dosing and monitoring while on CPB
Continue iv infusion: ≥2.5 mg/kg/h
Frequency of bivalirudin level monitoring: Every 30 min by ACT
Keep kaolin ACT >500 s (or at least 2.5 times baseline)
If <500 s, bolus 0.25 mg/kg and increase infusion by 0.25 mg/kg/h
Do not reduce infusion rate if ACT exceeds target
Performance considerations of CPB
Stasis in the CPB circuit should be avoided/minimized
Periods of hypothermia should be brief, and if possible only mild (30–34 °C) to prevent drug accumulation
Use recirculation limbs and keep cardioplegia circulating if containing blood
Avoid hemofiltration during CPB to avoid removal of bivalirudin
Management at the end of CPB
Careful consideration of the likely success of separation from CPB is necessary, and the anesthesia, perfusion, and surgical teams should agree upon the strategy for termination of the bivalirudin infusion
Stop infusion 10–15 min before weaning from CPB and then either: • Empty pump into the cell saver system to remove bivalirudin and replace with crystalloid • Add 50 mg bivalirudin to the pump circuit, keep the blood recirculating (may require a cross limb bridge between the venous and arterial lines), and initiate 50 mg/h infusion into the bypass circuit, which should be continued until such time as it is clear that the patient will not require urgent return to CPB
Ultra filtration by the perfusionist can remove approximately 70% of the bivalirudin from the patient
If separation from CPB does not occur within 20 min of stopping infusion, redose patient with 0.5 mg/kg and restart infusion at 2.5 mg/kg/h

Adapted from [30]

Table 11.9 Bivalirudin for off-pump coronary artery bypass grafting

Dosing of bivalirudin
Bolus of 0.75 mg/kg followed by continuous infusion of 1.75 mg/kg/h (stop infusion approx. 20 min before end of grafting); ACT: >300 s
Considerations of graft handling
Assessments of grafts for patency and leakage should be performed. Grafts should be flushed with saline
Stasis of the blood stream is associated with potential risk for thrombus formation in the graft and has to be strictly avoided

ACT activated clotting time

UFH and Platelet Inhibitors in Cardiac Surgery

Case series in patients with acute HIT requiring urgent cardiac surgery have reported use of UFH on CPB with platelet inhibitors to counteract HIT-related platelet activation. Platelet inhibitors used for this purpose include the prostaglandins epoprostenol and iloprost or the glycoprotein IIb/IIIa inhibitor tirofiban [22, 32, 33]. Iloprost and epoprostenol cause vasodilatation and hypotension, and the half-life of tirofiban is prolonged in patients with impaired renal function, with increased bleeding risk. These strategies could be justified in individual patients in whom bivalirudin is not indicated e.g., in complex procedures or in institutions with limited experience using bivalirudin.

Plasmapheresis Before Cardiac Surgery

Repeated therapeutic plasma exchange (TPE) (plasmapheresis) has been proposed to remove HIT IgG antibodies before urgent cardiac/vascular surgery in patients who have acute or subacute HIT [34]. However, it has been shown that repeated TPE achieves negative SRA despite ongoing strongly positive ELISA. This dissociation between the platelet activation assay and a PF4-dependent immunoassay for HIT antibodies indicates that patients with subacute HIT undergoing repeated TPE before heparin re-exposure should be tested by serial platelet activation assays even when their ELISAs remain strongly positive [35]. Case series of plasmaphereses before CPB until the anti-heparin/PF4 antibodies by ELISA became negative [36] were described with UFH during CPB without any HIT-related complications or excessive bleeding. Unresolved questions remain the timing of plasmapheresis, the kind of replacement fluid, HIT antibodies monitoring and postoperative anticoagulation. Moreover, HIT antibodies (IgG) are not as effectively removed by TPE as IgM, the procedure carries a high risk and it should be reserved as a

Table 11.10 Other interventions in heparin-induced thrombocytopenia (HIT) patients

	Bivalirudin	Argatroban
Transcatheter aortic valve implantation (TAVI), Mitraclip [37–39]	Intravenous bolus of 0.75 mg/kg followed by continuous infusion of 1.75 mg/kg/h	Not recommended
Ventricular assist devices (VAD) [41–46] HIT has been reported in 4.2% before and >10% after VAD implantation although the risk of HIT overdiagnosis is high HIT in VAD patients is associated with a higher risk for thromboembolic complications, especially thromboembolic stroke, but not pump thrombosis	During implantation: protocol for CPB After VAD implantation: Starting dose of 0.025 mg/kg/h followed by a mean dose of 0.040 ± 0.026 mg/kg/h targeting an APTT of 45–60 s	After VAD implantation: 0.02–0.4 μg/kg/min as starting dose, followed by 0.02–1.5 μg/kg/ min as maintaining dose achieving >1.5-fold APTT prolongation, but <100 s With a frequency of about 20% each, bleeding as well as thromboembolic events are common, but not more frequent compared to UFH in non-HIT patients

APTT activated partial thromboplastin time, *CPB* cardiopulmonary bypass, *UFH* unfractionated heparin, *VAD* ventricular assist device

last resort in only very special circumstances and not in subacute HIT.

Other interventions in which alternative anticoagulants have also been employed are percutaneous cardiovascular interventions such as transcatheter aortic valve implantation [37, 38]. MitraClip intervention [39, 40] and ventricular assist devices implantation [41–48] as reported in Table 11.10.

HIT in Children

Only limited data are available in children with case reports of bivalirudin use during CPB and argatroban for cardiac catheterization with perfusion and anticoagulation protocols [46].

Conclusion

HIT remains a commonly encountered iatrogenic complication of heparin therapy in hospitalized patients. In the nearly 6 decades since the initial descriptions of the disease, there have been major advances in understanding the pathogenesis of HIT, its varied clinical complications and treatment. Emerging anticoagulant therapies hold promise not only for the treatment of HIT but also in reducing its incidence.

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12

Tissue Sealants in Cardiac Surgery

Louis P. Perrault and Fatima Zohra Moukhariq

High Yield Facts

- Tissue sealants, adhesives, and hemostatic agents are second defense line against surgical bleeding.
- Topical hemostatic agents are divided into four classes: mechanical, flowable, fibrin, and active sealants.
- Mechanical hemostatic agents are physical barriers such as collagen, gelatins, and cellulose that are applied over the bleeding site.
- Flowable products are made of microfibrillar collagen and they are used to block blood flow at wound sites by turning fibrinogen into fibrin.
- Active products contain concentrated amounts of thrombin in order to cleave fibrinogen and form blood clots.
- Fibrin based sealants (e.g. Tisseel®) have great biocompatibility, biodegradability, elasticity, drug delivery, and low toxicity.
- Fibrin based sealants carry risk of viral transmission.
- Polyethylene glycol polymer products (e.g. Coseal®) are bioabsorbable and take 3 months to degrade.
- Polyethylene glycol polymer products swell up to 400% in the presence of moisture.
- Bovine serum albumin and glutaraldehyde (e.g. Bioglue®) products are affordable, easy to prepare, and have a 3-year shelf life at 25 °C.
- Albumin and glutaraldehyde products carry risk of toxicity due to glutaraldehyde degradation by-products and disease transmission due to the albumin coming from a bovine source.
- Thrombin gelatin matrix products (e.g. Floseal®) have the ability to conform to wound contours and to fill deep lesions.
- Thrombin gelatin matrix products carry the risk of disease transmission and swelling that might obstruct surrounding tissues.

Introduction

The use of anticoagulants and antiplatelet agents may increase the risk of anastomotic bleeding during cardiovascular surgery [1]. The perioperative and postoperative complications of such an event include blood loss, perianastomotic hemorrhage, pseudoaneurysm formation, the need for reoperation, and increased risk of acute graft thrombosis and failure [1]. Other consequences of bleeding are hemodynamic instability, impairment of visualization of the surgical field, prolonged clamping as well as procedure time [2]. The ramifications can be extreme such as increased mortality through the prevalence of the lethal triad known to be reached when acidosis, hypothermia, and coagulopathy occur simultaneously [2].

The first line of defense against bleeding during surgery involves the use of suture ligation, staples, cauterization, and the application of manual compression over the bleeding anastomotic edge with a gelatin sponge or other mechanical agents [1–3]. However, the manual pressure can result in tissue trauma, whereas sutures can cause further bleeding through the needle holes [2]. For this reason, there is a wide usage of tissue sealants, adhesives, and hemostatic agents as second defense line against surgical bleeding. The primary role of these tools is to complement sutures by allowing the

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riddance of body fluid leakage through needle holes, and providing superior abilities to withstand a stronger pressure at the site of wound closure [4].

Surgeons use these different agents to ensure reconnection of tissues and restoration of their original functions [5]. These surgical products differ in chemical composition, physical properties, as well as in the mechanism used to achieve their results [6]. For example, the general mechanism of tissue sealants consists of allowing healing via the formation of stable, elastic, long lasting, and insoluble chemical bonds in presence of water molecules [6]. Easy and fast application, excellent cosmetic results, unneeded suture removal, diminished pain, and minimal tissue trauma are the major advantages of the use of these products [5]. Another upside is their potential use in patients prone to bleeding with coagulopathy [4], hemophilia, and during urgent interventions for which it is not possible to wait for effects of anticoagulants to wear off.

Definitions and Classification of Topical Hemostatic Agents, Tissue Sealants, and Adhesives

Hemostatic agents prevent bleeding, but they do so by stimulating the coagulation cascade and forming a blood clot over the wound site [7]. Topical hemostatic agents are divided into four classes: mechanical, flowable, fibrin, and active sealants [8] (Table 12.1). Mechanical hemostatic agents are physical barriers such as collagen, gelatins, and cellulose that are applied over the bleeding site [7]. This matrix provides a platform for platelet aggregation and stimulates the extrinsic coagulation cascade for blood clot formation [7]. Flowable products are made of microfibrillar collagen and they are used to block blood flow at wound sites by turning fibrinogen into fibrin [8]. Active products contain concentrated amounts of thrombin in order to cleave fibrinogen and form blood clots [8].

Table 12.1 Classification of FDA approved topical hemostatic agents[#a]

Mechanical	Flowable	Fibrin/Synthetic	Active
Gelatin sponge (may be used with thrombin) Porcine gelatin • **Gelfoam** (Pfizer Pharmacia) • **Surgifoam** (Ethicon J&J) • **Gelfoam plus** (Baxter Healthcare Corp.)	Gelatin	Fibrinogen + thrombin (human pooled plasma) • **Tisseel** (Baxter) (Human pooled plasma thrombin, human pooled fibrinogen, synthetic aprotinin) • **Evicel** (J&J) (Human pooled plasma thrombin, human pooled fibrinogen, human albumin)	Bovine thrombin • **Thrombin-JMI** (King)
Collagen Bovine • **Avitene sheets** (non-woven web) (Davol) • **Ultrafoam collagen sponge** (Davol)	Gelatin matrix + thrombin • **Surgiflo** (J&J) (Porcine gelatin) • **FloSeal** (Baxter) (Bovine gelatin and human pooled plasma thrombin)	Cyanoacrylate Butyl cyanoacrylate + MS (GEM Srl) • **Glubran 2** (GEM)	Human pooled plasma thrombin • **Evithrom** (Omrix Biopharmaceutical)
Cellulose • **Surgicel** (J&J) • **Surgicel Nu-Knit** (J&J)			Recombinant thrombin • **Recothrom** (ZymoGenetics)
Chitin and chitosan-based hemostatic agents • **Celox** (SAM Medical Products) • **HemCon** (HemCon Medical Technologies Inc.) • **QuickClot** (Z-Medical Corp.)			
Polysaccharide spheres • **Arista** (Medafor)			

J&J Johnson and Johnson

B.Braun, Melsungen, Germany; **Baxter**, Deerfield, IL, USA; **Covidien**, Dublin, Republic of Ireland; **Cryolife**, Kennesaw, GA, USA; **Davol Inc.**, Warwick, RI, USA; **Ethicon**, Somerville, NJ, USA; **GEM Pharmaceuticals**, Birmingham, AL, USA; **Hemcon**, Portland, OR, USA; **Johnson & Johnson**, New Brunswick, NJ, USA; **King**, Bristol, TN, USA; **Medafor Inc.**, Minneapolis, MN, USA; **Omrix**, Jerusalem, Israel; **Pfizer**, New York City, NY, USA; **Sam Medical**, Wilsonville, OR, USA; **Z-Medical**, Roswell, GA, USA; **Zymogenetics**, Seattle, WA, USA

[a] [2–11]

Table 12.2 Classification of FDA approved tissue sealants[a]

Fibrin products	Albumin and glutaraldehyde	Polyethylene Glycol (PEG) polymer	Cyanoacrylate
Fibrinogen + thrombin • **Tisseel** (Baxter) (Human pooled plasma thrombin, human pooled fibrinogen, synthetic aprotinin) • **Evicel** (J&J) (Human pooled plasma thrombin, human pooled fibrinogen, human albumin)	45% Bovine serum albumin + 10% glutaraldehyde • **Bioglue** (Cryolife)	Two PEG polymers • **Coseal** (Baxter)	n-Butyl cyanoacrylate + n-Octyl cyanoacrylate • **Omnex** (Ethicon)
		PEG + Trilysine amine • **Duraseal** (Covidien)	

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[a][2–10, 12]

Table 12.3 Classification of FDA approved tissue adhesives[a]

Fibrin products	Albumin and glutaraldehyde	Cyanoacrylate
Fibrinogen + thrombin • **Tisseel** (Baxter) (Human pooled plasma thrombin, human pooled fibrinogen, synthetic aprotinin) • **Evicel** (J&J) (Human pooled plasma thrombin, human pooled fibrinogen, human albumin)	45% Bovine serum albumin + 10% glutaraldehyde • **Bioglue** (Cryolife)	Butyl cyanoacrylate + MS (GEM Srl) • **Histoacryl** (B. Braun) • **Glubran 2** (GEM)

J&J Johnson and Johnson

B.Braun, Melsungen, Germany; **Baxter**, Deerfield, IL, USA; **Covidien**, Dublin, Republic of Ireland; **Cryolife**, Kennesaw, GA, USA; **Davol Inc.**, Warwick, RI, USA; **Ethicon**, Somerville, NJ, USA; **GEM Pharmaceuticals**, Birmingham, AL, USA; **Hemcon**, Portland, OR, USA; **Johnson & Johnson**, New Brunswick, NJ, USA; **King**, Bristol, TN, USA; **Medafor Inc.**, Minneapolis, MN, USA; **Omrix**, Jerusalem, Israel; **Pfizer**, New York City, NY, USA; **Sam Medical**, Wilsonville, OR, USA; **Z-Medical**, Roswell, GA, USA; **Zymogenetics**, Seattle, WA, USA

[a][2–12]

Tissue sealants prevent leakage of fluids or blood from blood vessels and other structures without necessarily relying on the coagulation cascade [9]. In contrast, tissue adhesives, also known as glues, can attach blood vessels or two skin or muscle flaps together by creating bonds between tissues [9]. Sealants have four major types of products and some of them overlap with the three products found under the category of adhesives (Tables 12.2 and 12.3). The source of the different products in each category can be natural or biological, synthetic, and semi-synthetic [5]. The general qualifications sought in such useful tools in surgery is efficient adhesiveness, short compression time, immediacy of action, long shelf life, easy storage, nontoxicity, low cost, and short preparation time and application [2].

Clinical Use in Cardiovascular Surgery

Tissue sealants, adhesives, and hemostats are useful in cardiovascular surgery such as coronary artery bypass grafting, heart valve and aorta repair and replacement, heart transplant, aneurysm repair, and the placement of ventricular assist devices [6]. They are particularly used in procedures where there is a high risk of bleeding in surgeries such as aortic valve replacement, surgery for the ascending and descending aorta, patch plasty, carotid endarterectomy or in patients over 60 years old [2]. In the 2017 European guidelines for patient blood management for adult cardiac surgery, the routine use of topical sealants is not recommended [9]. For instance, the guidelines stipulate that they should not be considered in case of generalized bleeds but rather when the bleeds are localized and persistent [9].

The types of bleedings for which the use of these products can be handy are raw surface bleeds, oozing venous-type bleeds, bone bleeding, and needle-hole bleeding [2]. Moreover, they can be convenient when there is a highly friable tissue since the strain imposed by sutures to close the wound would cause further damage to the surrounding tissues without sealing the opening. Surgeons usually base the choice of the agent used on their preference and their experience with the particular product rather than evidence-base practice [2]. To help manage bleeding in surgery, a reference chart of some possible scenarios and the appropriate choice of agent is suggested for surgeons (Fig. 12.1).

Barnard and Millner published a review on topical agents used in cardiac surgery focusing predominantly on randomized controlled trials (RCTs). Table 12.4 is a summary of key RTCs from this review [13].

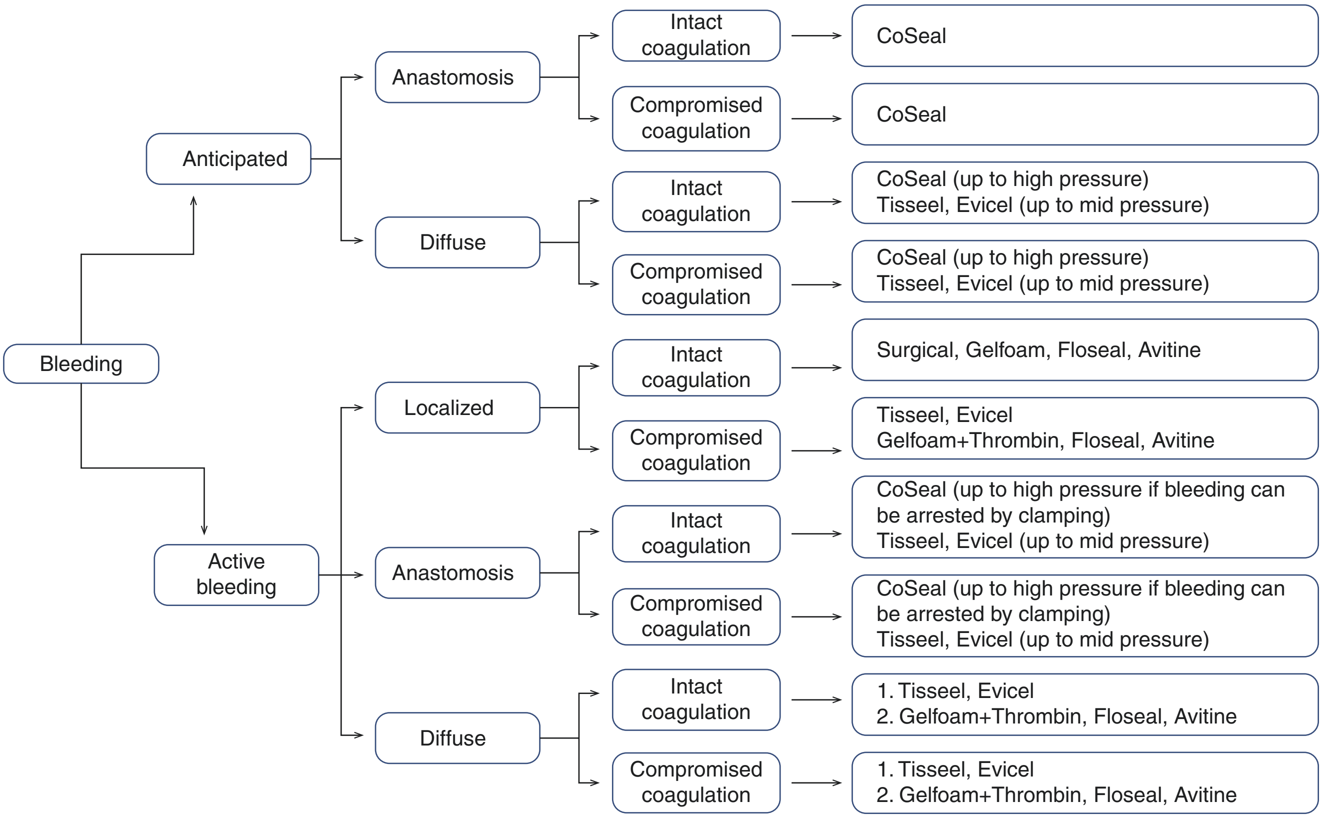
Bleeding
Anticipated
Active bleeding
Anastomosis
Diffuse
Localized
Anastomosis
Diffuse
Intact coagulation
Compromised coagulation
CoSeal
CoSeal
CoSeal (up to high pressure)
Tisseel, Evicel (up to mid pressure)
CoSeal (up to high pressure)
Tisseel, Evicel (up to mid pressure)
Surgical, Gelfoam, Floseal, Avitine
Tisseel, Evicel
Gelfoam+Thrombin, Floseal, Avitine
CoSeal (up to high pressure if bleeding can be arrested by clamping)
Tisseel, Evicel (up to mid pressure)
CoSeal (up to high pressure if bleeding can be arrested by clamping)
Tisseel, Evicel (up to mid pressure)
1. Tisseel, Evicel
2. Gelfoam+Thrombin, Floseal, Avitine
1. Tisseel, Evicel
2. Gelfoam+Thrombin, Floseal, Avitine

Fig. 12.1 Surgical scenarios in cardiovascular surgery [2]. (Adapted from Spotnitz, et al. [10])

Table 12.4 Summary of randomized controlled trials of hemostatic agents in cardiovascular surgery[a]

Agent	Control	Number	Outcome
Colgel	Surgicel	71[b]	Chest tube drainage in first 24 h was Colgel 373 ± 143 mL vs Surgicel 571 ± 144 mL ($p = 0.01$) and in the first 3 h it was 132 ± 41 vs 228 ± 57 mL, respectively ($p < 0.001$)
CoStasis[c]	Collagen sponges	72[b]	Bleeding controlled within 10 min with CoStasis 28/37 vs control 17/37; $p = 0.02$
Cyanoacrylate Sealant[c]	Oxidized cellulose	151[d]	Hemostasis mean time 119.3 vs 403.8 s ($p < 0.001$) and immediate hemostasis in 54.5% vs 10% in Cyanoacrylate Sealant and control, respectively
Tisseel[c]	Avitene/Surgicel	164[b]	92.6% bleeding control with Tisseel vs 12.4% with control agents at 5 min ($p < 0.001$)
Beriplast[c]	Surgery alone	52[e]	Fewer transfusions of FFP in the BP group compared with controls ($p \le 0.05$). BP group shorter time to achieve hemostasis ($p \le 0.05$), less bleeding intraoperatively ($p \le 0.01$)
CoSeal[c]	Gelfoam thrombin	54[f]	Immediate hemostasis in CoSeal 48 of 59 vs control 10 of 27 ($p = 0.002$)
BioGlue[c]	Surgery alone	151[g]	BioGlue bleeding (18.8% of anastomoses) vs control (42.9% of anastomoses; $p < 0.001$)
FloSeal[c]	Gelfoam thrombin	93[b]	FloSeal stopped bleeding in 94% of the patients (first bleeding site only) within 10 min compared with 60% in the control group ($p = 0.001$)
rThrombin[c]	bThrombin	164[d]	Hemostasis at 10 min 94% bThrombin, 91% rThrombin; p = NS

BP Beriplast fibrin sealant, *bThrombin* bovine plasma-derived thrombin, *FFP* fresh frozen plasma, *NS* not statistically significant, *rThrombin* recombinant thrombin

[a] [13]

[b] Cardiovascular procedures including re-do cardiac operations and ascending aortic aneurysm repair

[c] Studies sponsored by industry

[d] Peripheral vascular and arteriovenous procedures

[e] Procedures for congenital heart disease

[f] Implantation of Dacron grafts (DuPont, Wilmington, DE) for the repair of nonruptured aneurysms

[g] Cardiac and vascular repair procedures

Fibrin Sealants

Fibrin sealants are hemostats, adhesives, as well as sealants [9, 14]. They come from a biological source and are made of two basic components that are naturally occurring in humans and animals: fibrinogen and thrombin [4]. Both blood components are kept apart in one syringe with two barrels, which allow both components to interact solely at the moment of application. The action mechanism relies on the fact that the last step of the coagulation cascade is mimicked. Stable blood clots occur when thrombin cleaves fibrinogen into fibrin upon their contact with each other, which helps in wound healing and closure [3]. Within days or weeks, fibrinolysis dissolves the blood clots and no tissue inflammation is triggered since the sealant is entirely absorbed by macrophages and fibroblasts [1, 15].

Fibrin sealants lower risks of hemorrhage in patients who are undergoing a second cardiac intervention [6]. In ventricular assist devices surgery, the unavailability of presealed Dacron grafts results in the use of fibrin adhesive to seal prosthetic grafts [6]. During valve replacement, fibrin sealants containing antibiotics can be applied to the prosthesis as prophylaxis or treatment against bacterial endocarditis [6]. Promotion of blood clots formation via fibrin sealant is useful in off pump coronary artery bypass and minimally invasive direct coronary bypass since hemostasis can hardly be achieved through a small opening [6].

Advantages

Fibrin based sealants are the agents mostly used in cardiovascular surgery and across almost all types of surgeries. They have great biocompatibility, biodegradability, elasticity, drug delivery, and low toxicity [6]. These hemostatic agents can be applied to patients with coagulopathy or under the effects of anticoagulants since they already have all the required components to form blood clots independently from components generated by the patient's coagulation cascade [4].

Disadvantages

Fibrin based hemostatic agents deal with a broad range of bleeding circumstances [3], but they still carry their share of disadvantages. For instance, it is important to screen the source of thrombin and fibrinogen as there is a chance of disease transmission [1]. Virus-inactivated fibrin sealants were developed to avoid such eventualities, but they have poor bonding strength and a complex preparation procedure [5]. Acute thrombus formation leading to acute thrombosis at the operative site and distal embolization are also risks associated with the use of fibrin sealants [1]. The adhesiveness and mechanical strength of this type of sealants is greatly reduced when applied on wet surfaces [5]. For this reason, fibrin sealants should be applied with a carrier sponge or adjunct to sutures and staples [5].

Polyethylene Glycol Polymers

Polyethylene glycol polymers (PEG) are synthetic products that act as both sealants and hemostatic agents [15]. The two approved, marketed, and widely used products are Coseal® and Duraseal® [14]. Coseal® is mainly used for vascular surgery but can also be used to treat air leaks in thoracic surgery [14]. Coseal® comes with a common housing unit for two syringes, and a syringe clip that allows pushing out the content of both syringes simultaneously in the tip. This product is made of two PEG polymers, hydrogen chloride and sodium phosphate—sodium carbonate solutions [14] which form hydrogels that cross-link at the application site to promote tissue adhesion [8, 16]. Usually, PEG products require visible light to crosslink and increase intervention time significantly [15] but Coseal® overcomes this limitation on top of being a sealant stronger than fibrin based sealants [15].

Advantages

PEG products are bioabsorbable and take 3 months to degrade [5]. A study was conducted on aortic surgery patients to demonstrate the efficacy of Coseal® [7]. It was observed that Coseal® patients required significantly less red blood cells and fresh frozen plasma transfusions than the control group [7]. Moreover, Coseal® patients had lower postoperative chest drain volumes than the control group [7].

Disadvantages

Unfortunately, PEG products also have their share of disadvantages. The main concern with this category of products is the swelling of up to 400% with Coseal® in the presence of moisture [14, 17]. Surgeons using this product should consider the maximum swelling that might occur and be cautious about the possible damage to the surrounding anastomotic structures [17].

Albumin and Glutaraldehyde

Albumin and glutaraldehyde products are usually made of bovine serum albumin (BSA) , a glutaraldehyde activator, and formaldehyde [15]. Bioglue® by Cryolife is the only brand with FDA approval since it does not contain formaldehyde

[10]. Bioglue® is made of 45% purified BSA and 10% glutaraldehyde [18]. In surgery, bovine serum albumin-glutaraldehyde (BSAG) plays the role of a sealant as well as an adhesive [19]. The mechanism of action does not rely on the patient's coagulation cascade. Instead, BSAG polymerizes via crosslinking reaction between the aldehyde group in the glutaraldehyde and the lysine amine group supplied by BSA as well as by extracellular matrices or by cell surface proteins [19]. This product starts polymerizing after 30 s from its application and achieves high strength adhesiveness within 2 min [18, 19]. Unlike surgical sealants, BSAG requires priming before being applied via a dispenser gun or syringe [14]. The active components BSA and glutaraldehyde are kept apart in a dual chamber syringe system and mix at the correct ratio at the tip of the applicator [14, 16].

Albumin and glutaraldehyde products are useful in cardiovascular surgery. These products are employed in procedures such as aortic valve replacement, coronary artery bypass, and aneurysm repair of the abdominal aorta [15]. They are used particularly as sealants in large blood vessels anastomoses or as adhesives to reattach the intimal and adventitial layers in the repair of aortic dissection, aortic root, and arch reconstruction [9, 18].

Advantages

BSAG products are affordable, easy to prepare, and have a 3-year shelf life at 25 °C [14]. It has been reported in studies that this sealant lowers risks of reoperation and bleeding complications [19]. Moreover, it decreases blood utilization and has a long half-life of approximately 30 days [15, 19]. Conversely, many studies investigating safety concerns with this product were performed to look into organ embolization, tissue necrosis, pseudoaneurysm formation, nerve damage, tissue conduction trouble, and limitation of aortic growth [7–19]. Until now, studies have not found substantial evidence that BSAG causes pseudoaneurysm [19]. The study by Weiner et al. reports higher percentage of pseudoaneurysm in the non-glue group than the BSAG glued group [19].

Disadvantages

There is a risk of toxicity due to glutaraldehyde degradation by-products and disease transmission due to the albumin coming from a bovine source [14]. Like any glue, BSAG hardens, causing vessel stiffness, and decreases vessels elasticity and compliance [19]. Bioglue® was designed with less flaws than the common BSAG products such as not being cytotoxic, having the same stiffness as a healthy aorta and the ability to be applied in dry or wet environment [7].

Cyanoacrylates

Cyanoacrylates are synthetic adhesives and sealants that are commonly used to hold two skin edges together [14]. Some cyanoacrylate products might have hemostatic properties such as Histoacryl®, a tissue adhesive making small wounds closure possible. It was introduced in the late 1960s and along with the latest product, Glubran 2®, has been reported in more than 1000 clinical publications worldwide. Generally, cyanoacrylates are made of liquid monomers, which polymerize under 30 s in an exothermic reaction [15]. When applied, cyanoacrylates are exposed to anionic substances such as water or blood [5–15], resulting in a strong flexible bond made of long chains of polymers that holds the wound edges together [5].

Advantages

The upside of cyanoacrylates use is that they are waterproof, effective as fluid barrier, have excellent esthetic results, and they do not require wound dressing [4, 15]. Their greatest advantage is that they are bacteriostatic [16]. In addition, cyanoacrylates do not depend on the patient's coagulation state and can be used in case of coagulopathy [16]. Cyanoacrylates are usually less expensive than fibrin sealants and with the advancement in science, new formulas with less toxicity are emerging [16].

Disadvantages

Even though cyanoacrylates are the strongest adhesives and they create bonds that can last for few years, they are extremely cytotoxic [5, 20]. OMNEX® is an FDA authorized brand in cardiovascular surgery since the others are extremely cytotoxic for noncutaneous surfaces [5–21]. Unauthorized products can result in an acute and chronic inflammatory response [5–21]. Moreover, the human body is incapable of breaking these products down, resulting in the accumulation of their carcinogenous by-products in the tissue, cyanoacetate and formaldehyde [5, 15]. Another limitation is the restriction of the usual dynamic tissue movement since the instant solidification upon water exposure of this adhesive causes the formation of a rigid plastic-like seal that cannot accommodate the natural vascular motion [20].

Thrombin Gelatin Matrix

Thrombin gelatin matrix is a topical hemostatic agent that combines mechanical material (gelatin matrix) with an active component (thrombin) [5, 7]. Products in this group are classified according to the source of gelatin. For instance, Surgiflo®

gelatin comes from a porcine source and may or may not contain thrombin, whereas Floseal® is composed of bovine gelatin and human thrombin [9, 14]. The mechanism of action consists of the gelatin acting as mechanical barrier to obstruct the bleeding site and helps in promoting platelets aggregation [12]. Meanwhile, thrombin converts fibrin into fibrinogen [12]. The product must be applied to a wet field as it facilitates the conversion of fibrin and in turn the blood clot formation [8]. Both gelatin and thrombin come into two separate syringes and require mixing before application [14]. Once the paste is applied, a moist saline sponge should be used to apply a gentle pressure for 2 min to aid hemostasis [14].

Advantages

The upside of thrombin gelatin matrix products use is their ability to conform to wound contours and to fill deep lesions [12]. They also cause rapid hemostasis and have precise application [12]. Comparative studies have been performed to observe the effectiveness of Surgiflo® vs Floseal®. Floseal® demonstrated better results, faster hemostasis, reduction in complication and transfusions compared to Surgiflo® when used intraoperatively [12].

Disadvantages

The main concerns with this product are disease transmission and swelling that might obstruct surrounding tissues [14]. To avoid swelling, surgeons should remove excess product [14].

Cost Analysis at the Montreal Heart Institute

The total cost per year of hemostatic and biological products purchased at the Montreal Heart Institute is shown in Fig. 12.2. Over the last 10 years, the total cost of hemostatic and biological products quadrupled reaching $ 848,331. On the other hand, the total money spent on blood products in 2017 was $ 3,064,611 (Table 12.5). Also shown is the use of blood products that has decreased since 2013 (Fig. 12.3) and the use of hemostatic and biological products that has remained somehow more constant (Fig. 12.4). In addition, a cost analysis of re-exploration for bleeding after cardiac surgery demonstrated that the resource utilization costs were substantially higher in patients requiring re-exploration for bleeding and that included prolonged stays in the intensive care unit and blood transfusions [2].

Table 12.5 Total cost of blood products in 2017 at the Montreal Heart Institute

Blood products	Number of units	Cost per unit ($)	Annual cost ($)
Globular sediment PRC	3307	355	1,175,109
Cryoprecipitate	1324	157	208,371
Platelets (pooled and apheresis)	994	637	632,711
Frozen plasma	708	163	115,114
Apheresis platelet pack	33	435	14,362
Stable product transfused			761,865
Loss of labile products			157,079
Total			3,064,611

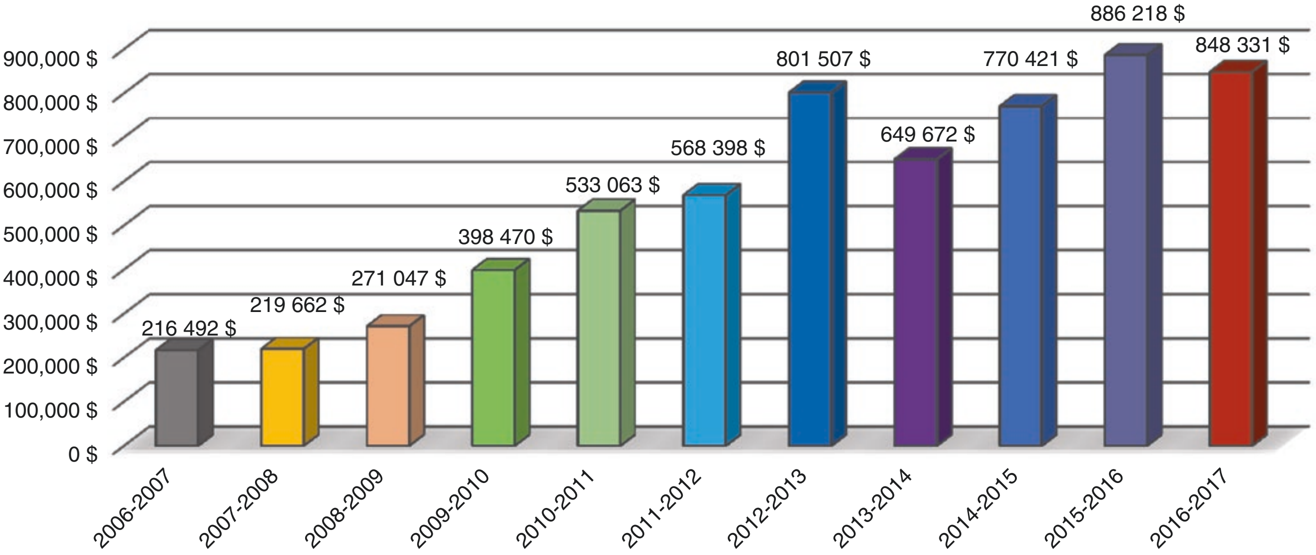

Fig. 12.2 Total cost per year of hemostatic and biological products purchased at the Montreal Heart Institute. (Adapted from Spotnitz, et al. [10])

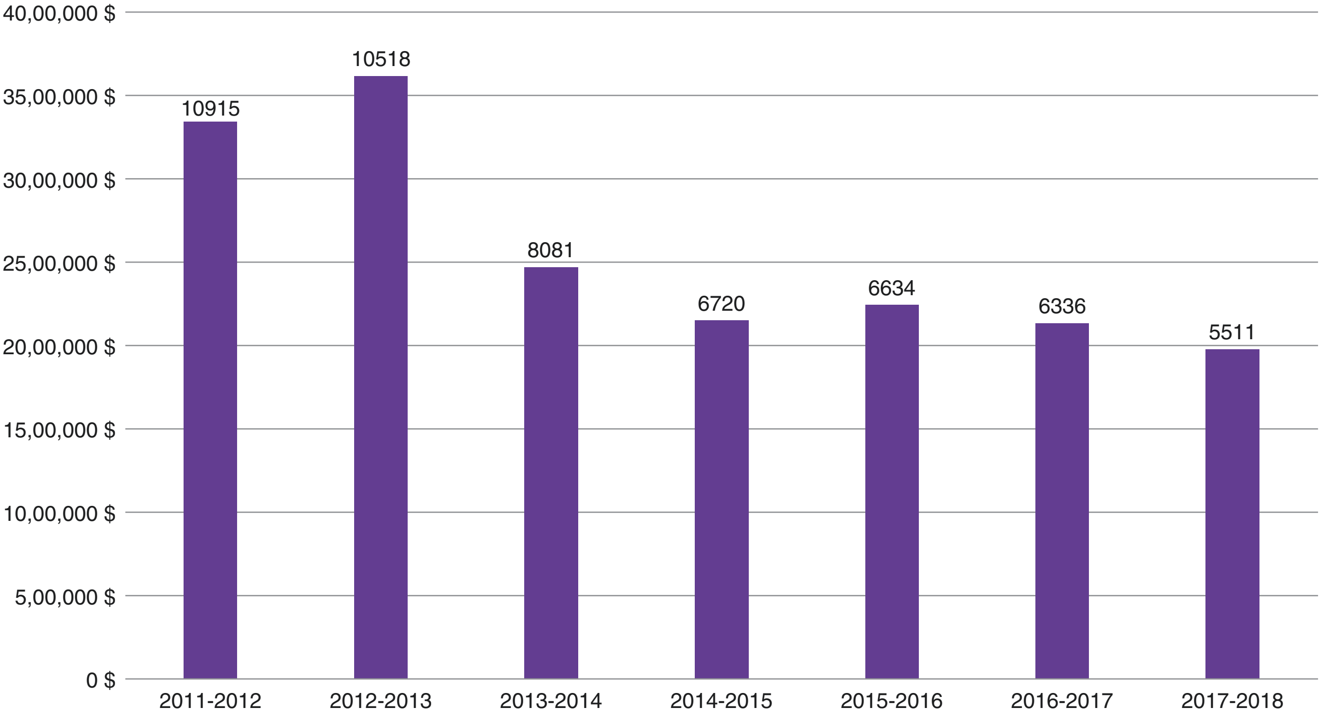

Fig. 12.3 Expenses and units: use of blood products, 2011–2018 at the Montreal Heart Institute. (Adapted from Spotnitz, et al. [10])

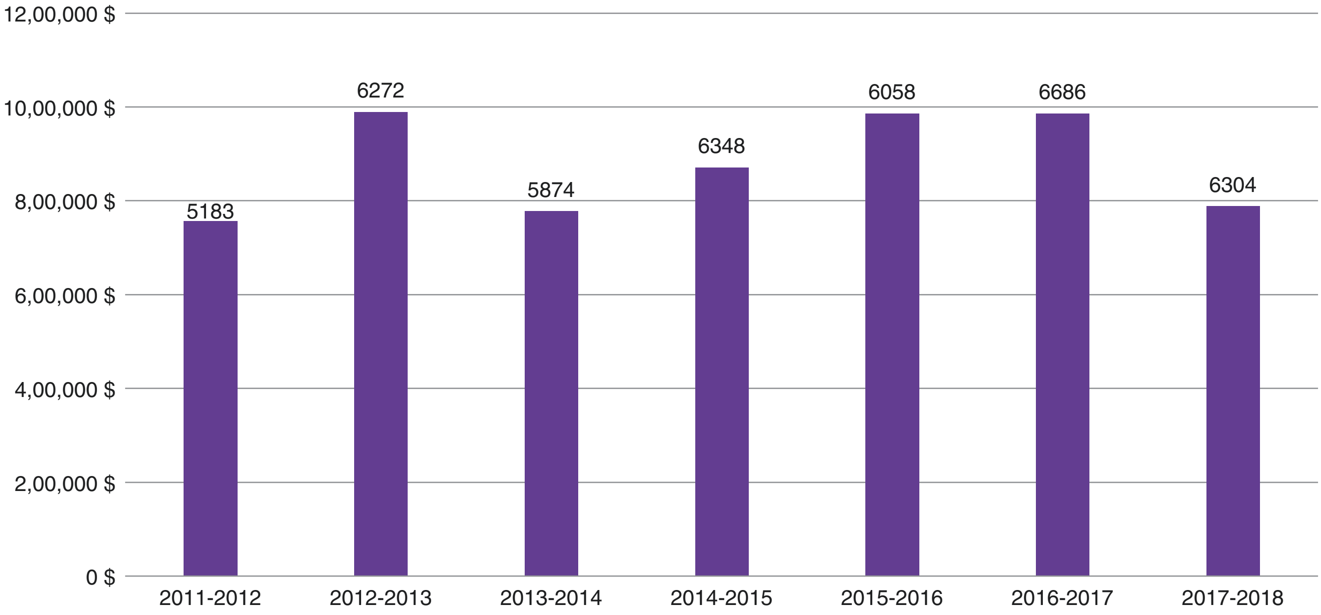

Fig. 12.4 Expenses and units: use of haemostatic and biological products, 2011–2018 at the Montreal Heart Institute. (Adapted from Spotnitz, et al. [10])

Conclusion

Topical hemostatic agents, tissues sealants, and adhesives are used in cardiovascular surgery as a second line of defense against bleeding. Several brands with different composition and properties are at the surgeons' disposal. It is important for surgeons to be aware of these products advantages, disadvantages and application methods to avoid future complications. Even though these products are effective in reducing costs and bleeding complications, no product on the market is currently completely devoid of disadvantages and limitations [22].

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Part II

Coronary Artery Disease

Conduits for Coronary Artery Bypass Surgery

13

Cristiano Spadaccio and Mario F. L. Gaudino

High Yield Facts

- Coronary artery bypass grafting (CABG) has become one of the mainstays in the treatment of ischemic heart disease.
- Both arterial and venous conduits and a variety of their combination can be used in CABG.
- Arterial conduits available are left internal thoracic artery (LITA), right internal thoracic artery (RITA), radial artery (RA), and right gastroepiploic artery (RGEA).
- Pedicled or skeletonized harvesting techniques have been described for arterial conduits. Skeletonization of ITAs has been suggested to reduce the risk of sternal wound complications.
- Minimally invasive endoscopic harvesting can be applied to RA and long saphenous vein.
- Use of a "no-touch" technique for saphenous vein grafts (SVG) preserving the tissue surrounding the vessel (no-touch technique) has been suggested to improve patency rate by minimizing vascular trauma but can increase risk of wound infection and bleeding.
- Biological augmentation or physical reinforcement of SVG has been suggested but long term results are awaited.
- Composite arteriovenous conduit obtained by anastomosing SVG to LITA to graft non-left anterior descending coronary (LAD) territories has been shown to have satisfactory short and mid-term outcomes, but more confirmatory evidence is required.
- Arterial grafting, in particular LITA, to the LAD is well established on the basis of its prognostic benefit.
- The choice of the second and further conduits for the remaining targets remains debatable, but on the basis of the evidence currently available and on the basis of the long-term results of previous and new randomized controlled trials (RCTs), a multiple arterial grafting strategy should be the preferred approach in the majority of the patients.

Introduction

Coronary artery bypass grafting (CABG) has progressively become one of the mainstays for the treatment of ischemic heart disease since its first introduction in 1967 by Rene Favaloro. Surgical myocardial revascularization can be achieved using different conduits, namely left internal thoracic artery (LITA), right internal thoracic artery (RITA), radial artery (RA), right gastroepiploic artery (RGEA) and saphenous vein (SV). A variety of their combinations have been described.

This chapter will individually examine the characteristics of each of the conduits and the results obtained over the course of 50 years of CABG experience.

Internal Thoracic Artery

The LITA originates from the subclavian artery and supplies the sternum and the breasts before continuing after its bifurcation as the superior epigastric and musculophrenic arteries.

From the histological standpoint, LITA is characterized by discontinuous internal elastic lamina and a thin media

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enriched by multiple elastic laminae in the absence of a significant muscular component. These characteristics, along with the biological findings of an increased production of vasoactive molecules and antiinflammatory cytokines [1], are thought to be at the root of the largely superior patency rate of this conduit when compared to the others. In fact, the reduced tendency for spasm due to the lack of significant muscle layer, and the relative protection from the development of atherosclerosis guaranteed by its biological properties, could explain the superior outcomes reported for this conduit [2].

The LITA can be harvested in a skeletonized or pedicled fashion, with the first technique being thought to carry the advantage of increasing the effective length of the conduit available for grafting (normal length ranging from 14.32 to 19.48 cm) [3] and of avoiding extensive devascularization of the sternum, with potential implications for the sternotomy healing process. In this regard, skeletonization of ITA has been reported to reduce the risk of deep sternal wound infections also in diabetic patients, normally more prone to this type of complications [4, 5].

More than 30 years after the pioneering work at the Cleveland Clinic on arterial CABG [6], the prognostic benefit of LITA grafting on the left anterior descending (LAD) artery and its superiority in comparison to other conduits is well established. Large studies on the long-term outcomes of LITA have shown more than 90% patency rate at 20 years [2, 7] using this conduit on LAD. These results were confirmed when LITA was anastomosed to circumflex artery (patency of 97% at 5 years, 92% at 8 years, 89% at 10 years and 91% at 15 years), whilst its patency was reduced to 84% at 15 years when grafting the right coronary artery [7]. The reasons of the performance discrepancy seen when LITA is anastomosed on the left or right system are probably due to the size mismatch of the vessels and the different rate of disease progression at the crux [8]. However, these results still outperform the patency rate of saphenous vein grafts (SVG), which dramatically falls below 75% at 10 years follow-up [9]. The right ITA demonstrated a patency rate spanning around 90% on the left system and between 80–90% on the right system at 10 years [10]. The histomorphological differences demonstrated between the right and the left ITA partly might explain this discrepancy in outcomes.

The Radial Artery

The radial artery (RA) arises from the bifurcation of the brachial artery in the antecubital fossa. It runs distally on the anterior part of the forearm ending in the deep palmar arch, where it joins with the deep branch of the ulnar artery. In the preoperative assessment, the anastomosis among the radial and ulnar system is assessed by the Allen's test which proves the collateralization of the two systems and therefore the functional compensation of the ulnar artery if the radial artery is harvested as conduit for CABG. However, this test has been shown to be unreliable and more objective methods of ulnar compensation are needed, such as Doppler ultrasound and percutaneous oximetry [11, 12].

Histologically, the RA is characterized by a well-developed muscular profile which had initially cast some shadows on its use in CABG because of concerns regarding vasospasm once implanted in the coronary system. This issues conspired against RA use for a prolonged period of time since its initial introduction in the 70s [13], before being reintroduced in the early 90s [14]. For this reason calcium channel blockers with or without long-acting nitrates have been widely used in the postoperative management of these patients [15]. However, biological studies demonstrated a progressive remodeling towards a more elastomuscular phenotype after implantation as graft [16] and clinical reports denied a benefit of antispastic pharmacological therapy [17].

Angiographic studies have demonstrated patency rate of 80–90% at 7–10 years follow-up [18]. A more recent study reported an 84.4% patency rate at 20 years with a probability of graft failure at the same time point similar to LITA (19.0 ± 0.2% for LITA vs 25.0 ± 0.2% for the RA) [19].

The RA might be harvested in skeletonized or pedicled fashion with an open or endoscopic technique. Despite some proposing an advantage in conduit length and diameter if harvested in skeletonized fashion [20], others pointed out the longer harvesting time and the risk for endothelial damage, especially when harmonic scalpel is used [21]. Considering the lack of clear evidence of a significant improvement in patency rate using the skeletonization technique, this approach should be discouraged [11]. However, the success of RA use in CABG does not seem to be dependent either on the effect of an open incision or a minimally invasive endoscopic approach. Conversely, the degree of coronary stenosis influences the long-term patency rate, with vessel stenosis >70% being considered the only indication for RA grafting and stenosis of 90% being associated with even better results [22]. Despite apparent better results on the right coronary system, location of target vessel and site of proximal and distal anastomosis did not significantly influenced the patency rate in a large angiographic study at 6.5 years [23] and 20 years follow-up [19].

At least six randomized clinical trials and several observational studies have compared patency rate and outcomes of RA versus RITA and SVG and very recent evidence from a large patient-level meta-analysis has decreed the "renaissance" of RA [24]. When compared to SVG, randomized trials and meta-analyses have showed significantly higher patency rate and lower incidence of clinical events [22, 25–32]. With respect to RITA, the RAPCO (Radial Artery Patency and Clinical Outcomes) trial demonstrated no difference in the patency of the two conduits with a trend towards improved event-free survival in the RA group at the 6-year follow-up [27]. A meta-analysis including both RCTs and observational studies demonstrated comparable mortality but reduced incidence of cardiac events in the RA group [33]. However, a comparative network meta-analysis on angiographic outcomes demonstrated a non-significant 27% absolute risk reduction for late functional graft failure in the RITA as compared with RA [32]. From a practical perspective, it has been suggested that RA might be a better option in patients at increased risk for post-operative sternal complications. Hoffman et al. and Tranbaugh et al., in two separate propensity matched studies, supported the benefit of RA use in patients at risk of sternal complications [34, 35]. The easily tolerable harvesting also in frail patients and the avoidance of additional sternal devascularization are the perceived advantages of RA use [33]. Additionally, a sub-analysis of the RAPS (Radial Artery Patency Study) on diabetic patients even described a significant risk reduction of graft occlusion using RA in these patients [22], making the use of this conduit in diabetics particularly attractive.

The Right Gastroepiploic Artery

The right gastroepiploic artery (or right gastro-omental artery) is one of the two terminal branches of the gastroduodenal artery, running along the greater curvature of the stomach, between omental layers and eventually anastomosing with the left gastroepiploic artery from the splenic artery.

Histologically, despite sharing the same wall thickness with ITA [36], the RGEA contains many smooth muscle cells in the media, suggesting potential concerns of spasmogenicity during surgical manipulation [37].

First use of RGEA in CABG settings was independently described in 1987 by Pym et al. [38] and Suma et al. [39]. Early hemodynamic studies by Takayama et al. showed that harvested RGEA maintained its physiological behavior after exercise or digestion [40] and retained good flow capacity after endothelial stimulation with vasoactive substances [41]. Also, it was found to suffer very low incidence of severe atherosclerosis [42].

In clinical settings, RGEA is readily available and large angiographic studies on anatomical length and diameter of the conduit demonstrated 97% and 88% probability to reach right coronary and circumflex artery, respectively. Few contraindications have been described suggesting availability of RGEA for every case without the need for a preoperative angiographic evaluation [43]. Similarly, no increase in perioperative risk was identified when compared to patients in which RGEA was not utilized [44].

Because of the anatomical situation, the most favorable target for the in-situ RGEA graft is the distal right coronary artery, although distal circumflex can also be grafted with this conduit. However, a sub-occlusive (>90%) stenosis of the target vessel is recommended to maximize patency rates and avoid spasm or competitive flow issues [45]. In a recent review of evidence and experience with RGEA over 30 years, Suma et al. described patency rate of 97% in the short term and 90% at 10 years, especially using skeletonized harvesting technique and selecting target vessels with >90% stenosis [37, 46]. Despite a network meta-analysis of randomized controlled trials reporting a higher graft occlusion risk of RGEA compared to other conduit [32], 5-, 10- and 15-year actuarial survival rates have been described as 91.7%, 81.4%, and 71.3%, respectively, in a large series with a 20-years follow-up [47]. Moreover, superiority in terms of late survival with the use of RGEA instead of SVG has been reported in two separate series [48, 49]. Proponents of its use advocate the importance of the skeletonized technique [46] and the selection of targets as reliable precautions to achieve success [37], despite the majority of the currently available literature focusing on pedicled RGEA. Only few studies have compared RGEA with RITA [50, 51] providing limited information to draw comprehensive conclusions in this context.

The Saphenous Vein

The great saphenous vein (or "long saphenous vein") is a large, subcutaneous, superficial vein of the leg, running along the length of the lower limb and returning blood to the deep femoral vein at the femoral triangle. Presence of valves necessitates its use in a reversed fashion when used as a coronary bypass graft. From the biological and histological point of view, several differences have been described in comparison to ITA including the intrinsic structure, the reduced production of endothelial nitric oxide and the impaired secretory pattern of cytokines after implantation in the coronary system [2, 52–54]. Since the initial studies by Motwani and Topol [52], the differences in biology and the impact of harvesting technique have been considered the main factors responsible for the incidence of graft failure (both acute and chronic) and the disappointing long-term patency rate (75% at 18 months [52, 55].

Over the years, a significant amount of experimental efforts have focused on minimizing trauma during harvesting or to enhance biological properties of the vein. Souza described the no-touch technique in 1996 in which the dissection of

SVG is performed leaving its surrounding tissue in-situ [56]. This method is thought to prevent spasm associated with adventitial denudation during harvesting, inhibit smooth muscle cell activation [57], and preserve integrity of vasa vasorum and endothelial function [58]. The results of a recent randomized trial showed superiority of this technique over the standard harvesting in terms of long-term patency with rates comparable to ITA [59]. However, the advantage of this technique in terms of conduit integrity preservation and future patency rate is counterbalanced by the increased potential for wound infection and bleeding related to the greater "invasiveness" of the procedure [60].

The saphenous vein can also be harvested endoscopically, with the benefit of avoiding large leg incision, wound healing problems and pain, especially when the median saphenous nerve is accidentally damaged during harvesting [61, 62]. Initial concerns about patency of SVG harvested endoscopically were raised in a large observational study in which this technique was associated with vein graft failure and adverse clinical outcomes [63]. The reasons underlying these findings were found in potential structural damage during harvesting [64]. Despite a meta-analysis confirming these results [65], there is no consensus on the inferiority of endoscopic SVG harvesting [62, 66]. A sub-analysis of the large Veterans Affairs Randomized On/Off Bypass (ROOBY) trial also showed lower SVG patency rate in the off-pump group [67]. It is expected that the results of a large angiographic study, the REGROUP trial (Randomized Endo-Vein Graft Prospective) will potentially shed light on this issue.

Another interesting approach has been introduced by Kim et al. in the SAVE-RITA trial which compared the outcomes of RITA with SVG anastomosed as Y graft on the LITA and used to graft both the left and right system. The rationale underlying this study relies on the fact that SVG anastomosed to the LITA would undergo reduced circulatory stress compared to the anastomosis on the ascending aorta and would be continuously exposed to endothelium-protective substances such as nitric oxide produced by the LITA [68, 69]. Additionally, avoidance of aortic cross clamp for proximal anastomosis could reduce the risk of stroke and aortic dissection. Conversely, sparing of RITA might decrease the chances of sternal wound infection while preserving this conduit in case of future redo surgery. One-year angiographic results showed non-inferiority of the saphenous vein composite graft to the RITA composite graft [70]. Five-years results have demonstrated similar positive findings, however, as recently reported, more evidence is needed to confirm the non-inferiority of composite arteriovenous conduits for CABG [71].

Biological augmentation methods to improve SVG resistance to atherosclerosis and failure have also been proposed. In this context the PREVENT IV trial investigated the role of ex-vivo treatment with edifoligide, an E2F decoy that regulates expression of genes controlling smooth muscle cells proliferation and potentially prevents neointimal hyperplasia. However, this was ineffective in the prevention of early vein graft failure [72].

Another strategy available to improve SVG outcomes entails the use of external stenting of SVG with the aim of preventing pressure-induced wall stress and reactive neointimal hyperplasia. Despite clear preclinical evidences, the clinical results are conflicting as yet [73]. A nitinol-based mesh (SVS® external venous nitinol mesh, Kips Bay Medical, Minneapolis, USA) has not produced encouraging results at 1-year (patency rate of reinforced SVG 76% versus non reinforced SVG 100% and arterial grafts 100%) [74]. However, newer technologies, such as the VEST device, a cobalt chromium external stent (VEST, Vascular Graft Solutions, Tel Aviv, Israel) have been associated with comparable patency to non-stented grafts [75] and significant improvements in haemodynamic flow within the stents [76]. Ongoing studies will determine whether this translates into superior graft patency over the longer term.

Grafting Strategy and Conduit Choice

LITA is always anastomosed to the LAD on the basis of the widely established prognostic benefit of this strategy. As for the second and subsequent grafts, several combinations and strategies are available. These can be broadly grouped in to a single or multiple arterial strategy. In the first, vein grafts are used for the remaining targets of the left and right system, in the latter, a second arterial conduit such as RITA, RA or RGEA can be used to graft the remaining targets on both the right and left side, or just on the left side, using an SVG on the right system.

On the basis of the evidence currently available and in accordance with the long-term results of previous and new RCTs [77], a multiple arterial grafting strategy should be the preferred approach in the majority of the patients and an *ad hoc* decisional algorithm has been recently proposed (Fig. 13.1) [78].

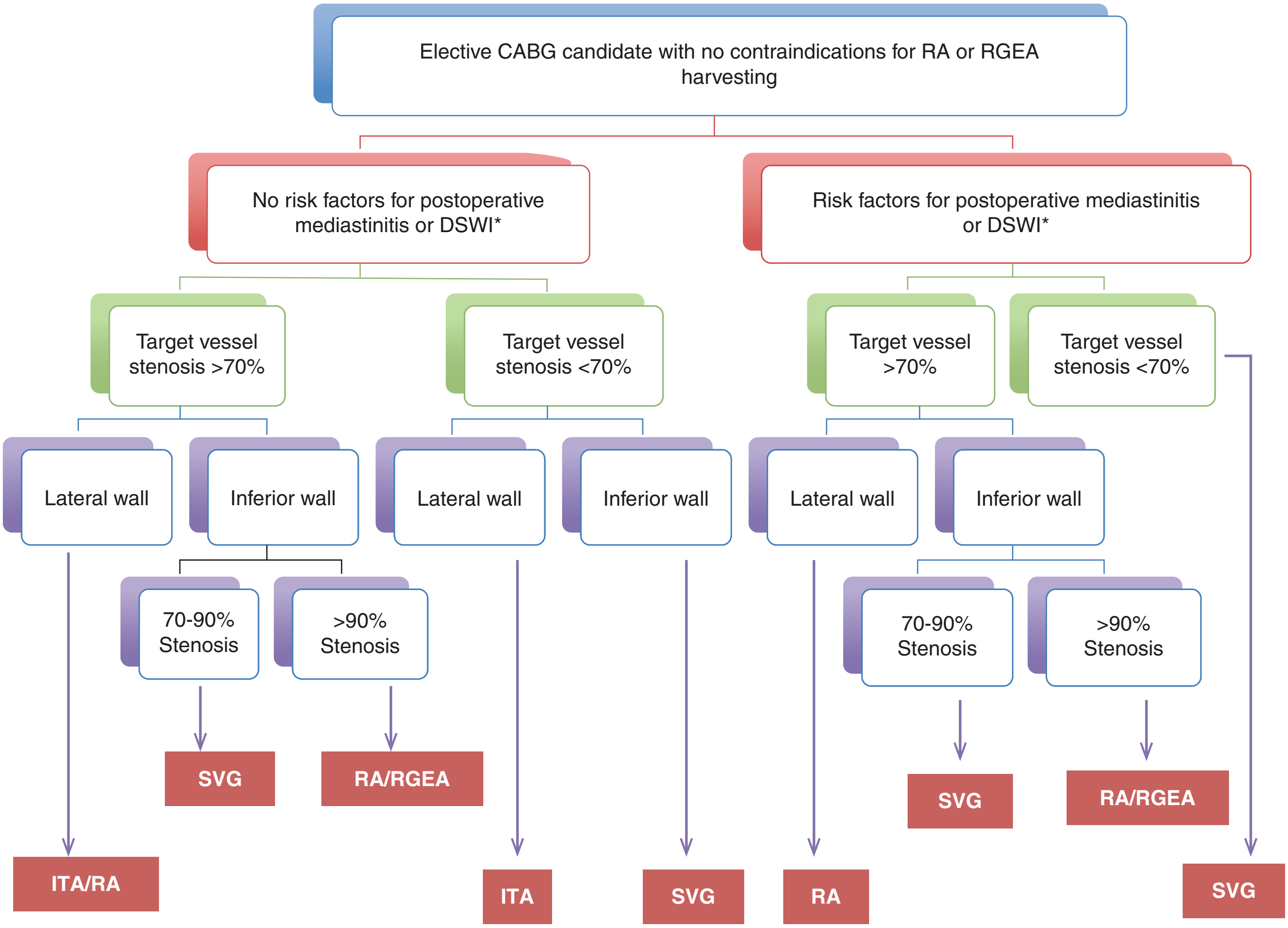
Elective CABG candidate with no contraindications for RA or RGEA harvesting
No risk factors for postoperative mediastinitis or DSWI*
Risk factors for postoperative mediastinitis or DSWI*
Target vessel stenosis >70%
Target vessel stenosis <70%
Target vessel >70%
Target vessel stenosis <70%
Lateral wall
Inferior wall
Lateral wall
Inferior wall
Lateral wall
Inferior wall
70-90% Stenosis
>90% Stenosis
70-90% Stenosis
>90% Stenosis
SVG
RA/RGEA
SVG
RA/RGEA
ITA/RA
ITA
SVG
RA
SVG

Fig. 13.1 Decisional algorithm for CABG. In the choice of grafting strategy particular attention should be given to technical, anatomic, and angiographic determinants of arterial conduit patency, as well as the clinical characteristics of the patient (morbid characteristics, diabetes, obesity, respiratory problems, steroid or immunosuppression treatments, especially if they occur simultaneously). Suggested conduit for the anterolateral wall are the RA and RITA, with the first being preferable in cases at risk for sternal complications and the second in patients without ulnar compensation. It is important to remember that RA can be used in sequential anastomosis being able to reach every distal vessel, however it is recommended for subocclusive target stenosis as more sensitive to competitive coronary flow than the RITA. The skeletonized in-situ RGEA can be used to graft the distal branches of the right coronary artery when critically stenosed (>90%). SVG is mainly considered for inferior wall lesions in case arterial conduit grafting is not feasible on clinical or technical grounds. (Note: In this algorithm no composite or elongated grafts are considered.) ∗Obesity, diabetes and severe chronic lung disease, especially in combination. *CABG* coronary artery bypass graft, *RA* radial artery, *RGEA* right gastroepiploic artery, *ITA* internal thoracic artery, *SVG* saphenous vein graft

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14

Endoscopic Saphenous Vein and Radial Artery Harvesting

Fabrizio Rosati and Gianluigi Bisleri

High Yield Facts

- Minimally invasive endoscopic saphenous vein and radial artery harvesting techniques are safe and effective approaches leading to a significant reduction in post-operative pain, wound and neurological complications, and increased patients' satisfaction.
- Endoscopic vessels harvesting is not associated with a higher incidence of graft failure or cardiac-related events.
- The technique utilized (sealed or non-sealed system) during minimally invasive endoscopic graft procurement can influence the degree of trauma to the conduit.
- Endoscopic harvesting should be performed by experienced operators in order to minimize conduit damage.
- Minimally invasive endoscopic radial artery and saphenous vein harvesting should be adopted as standard of care.

Introduction

Minimally invasive endoscopic saphenous vein (SV) and radial artery (RA) harvesting gained popularity in the last decade as an alternative to open techniques for grafts procurement during coronary artery bypass grafting (CABG). Open techniques are associated with excellent outcomes in terms of graft quality and patency rate but also lead to complications such as wound healing, pain and discomfort. Conversely, a minimally invasive approach for RA or SV harvesting is associated with less morbidity and discomfort without affecting long term outcomes in patient undergoing CABG [1].

Currently, minimally invasive endoscopic conduit harvesting for CABG can be performed using sealed and non-sealed systems. With sealed systems, the dissection tunnel is actively insufflated with carbon dioxide (CO_2) gas at 5–15 mmHg pressure while the device entry site is "sealed" in order to avoid gas leakage, maintain a target pressure throughout the entire procedure and improve exposure during harvesting. Conversely, non-sealed systems do not require active CO_2 insufflation to achieve endoscopic visualization; however, CO_2 may be used as a visual flush without using any occlusive port at the entry point, thus avoiding any pressurization in the dissection tunnel [2]. While both systems could be used for saphenous vein and radial artery conduits harvesting, in this chapter the authors will extensively describe the use of a non-sealed approach for SV and RA endoscopic harvesting.

Evidence

Different endpoints such as wound complications, neurological disturbances (including pain), patient satisfaction, graft quality, graft occlusion and major cardiac adverse events (MACEs) have been extensively analyzed in literature when comparing a traditional "open" harvesting technique with an "endoscopic" approach [3].

Graft Quality, Graft Occlusion and Major Cardiac-Related Events

Potential vessel injury associated with endoscopic vessel harvesting has been previously investigated. However, to date, no standard parameters to report the degree of damage have been adopted. It should be stressed that macroscopic (visually detectable) or microscopic injury (assessed by means of histology and/or functional evaluation of vasoreactivity or molecular expression changes) can occur during harvesting. Moreover, even the degree of experience of the operator and storage solution for the harvested conduit could

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potentially play an important role although these have been poorly investigated so far [4, 5].

When macroscopic damage is considered after SV harvesting, both techniques demonstrate similar results in terms of conduit quality (visually graded as good, fair or poor), length and proportions of veins requiring repair [6–8]. When microscopic analysis was performed, similar results were obtained when open versus endoscopic techniques were compared in terms of structural and functional viability of graft endothelium [6, 9–11]. However, the use of a sealed system for endoscopic SV harvesting is associated with a significant incidence of graft thrombosis [12]; thus, it is now recommended to administer heparin before saphenous vein procurement by means of a sealed-system or the adoption of open non-sealed system to reduce the likelihood of such a complication. Furthermore, the use of a sealed system has a potential detrimental effect on functional and structural properties of the SV endothelium and such changes seem to be significantly reduced when a non-sealed approach is used [13].

Macroscopic quality of RA is similar between "open" versus endoscopic harvesting techniques [6, 14, 15] as well as in terms of microscopic properties such as vasoreactivity and endothelial integrity [16, 17]. However, detrimental effects on RA integrity were demonstrated when a sealed approach was compared with non-sealed system for RA harvesting [18].

Recent reports raised concerns in terms of graft occlusion and major cardiac-related events following endoscopic vessel harvesting. In the PREVENT IV trial [19], a higher incidence of vein graft failure was demonstrated in patients undergoing endoscopic SV harvesting. Similarly, the ROOBY trial [20] showed a reduced SV patency at 12 months when a minimally invasive approach was used. However, these results were obtained from trials which were designed to investigate clinical outcomes following endoscopic vein harvesting versus or open technique and any insight was obtained with a secondary post-hoc analysis [21]. Another major drawback of these studies is the complete lack of information about device used for SV endoscopic harvesting in ROOBY trial, while in the PREVENT IV trial a sealed system was used in 85% of cases. Arguably, no patients received heparin before starting endoscopic SV harvesting procedure thereby contributing to further sub-optimal results in terms of graft patency.

Conversely, only few studies to date have reported graft patency following endoscopic RA harvesting with comparable results between an open and endoscopic approach at long-term follow-up [22, 23].

The most recent Consensus Statement from the International Society for Minimally Invasive Cardiothoracic Surgery analyzed outcomes for EV harvesting and endoscopic RA harvesting and concluded that there are no significant differences in terms of MACEs (myocardial infarction, reintervention for angina or reinfarction, all-cause mortality and angiographic patency) when endoscopic harvesting of these vessels is compared with the standard "open" techniques [1].

Wound and Neurological Complications and Patients' Satisfaction

Minimally invasive techniques have shown a significant advantage compared to the open approach when the incidence of complications is taken into account. In fact, especially for "open" techniques during SV harvesting, wound complications such as infection, cellulitis, dehiscence, delayed healing, drainage, lymphangitis, sepsis, can occur with a considerable higher incidence (from 2% to 25%) [24–37] (Table 14.1).

Moreover, open SV harvesting is associated with a higher degree of postoperative pain leading to delayed ambulation and neuropathy thereby leading to prolonged recovery. Notably, some studies have reported that the discomfort related with the leg incision at the harvest site can potentially be more relevant than the sternotomy-related discomfort [26].

Table 14.1 Randomized controlled trials comparing endoscopic and open vein harvesting technique

First author, publication year, [Ref]	Study period	No. of patients	Follow-up duration	Wound infection	NIWHD	30 day-mortality	Graft patency
Andreasen, 2008, [28]	2004–2007	132	5 and 30 days	OVH > EVH	OVH > EVH	OVH = EVH	NM
Au, 2008, [29]	2005–2006	120	30 days	OVH > EVH	OVH > EVH	OVH = EVH	NM
Schultz, 2006, [30]	2003–2004	200	30 days	OVH = EVH	OVH = EVH	OVH = EVH	NM
Yun, 2005, [31]	2000–2002	200	6 months	OVH > EVH	OVH > EVH	OVH = EVH	OVH = EVH
Perrault, 2004, [32]	2000–2002	40	3 months	OVH = EVH	OVH = EVH	OVH = EVH	OVH = EVH
Allen, 2003, [33]	1998	112	5 years	OVH > EVH	OVH > EVH	OVH = EVH	OVH = EVH
Bonde, 2002, [34]	2000	60	30 days	OVH > EVH	OVH > EVH	OVH = EVH	NM
Schurr, 2002, [35]	2002	140	30 days and 3 months	OVH > EVH	OVH > EVH	OVH = EVH	NM
Kiaii, 2002, [36]	1997–1998	144	6–8 weeks	OVH > EVH	OVH > EVH	OVH = EVH	NM
Hayward, 1999, [37]	1997	100	Hospital discharge, 3 weeks, 6 weeks	OVH = EVH	OVH = EVH	OVH = EVH	NM

EVH endoscopic vein harvesting, *OVH* open vein harvesting, *NA* not available, *NIWHD* non-infective wound healing disturbances, *NM* not measured

Similarly, when the overall incidence of complications is taken into account after endoscopic RA harvesting (such as wound dehiscence, infection, cellulitis and hematoma, pain, mobility and sensory dysfunction), the minimally invasive technique is superior to an open approach and is associated with significantly higher patients' satisfaction [38, 39]. Interestingly, endoscopic RA harvesting can also lead to a significant reduction in patients' discomfort (affecting work or daily activities even up to 6–9 months of follow-up) when compared to open RA harvesting [1, 40].

In conclusion, as recently reported by the most recent consensus statement from the International Society for Minimally Invasive Cardiothoracic Surgery, endoscopic approach is recommended as standard of care for vessels harvesting [1].

Patient Selection

An endoscopic approach can be potentially performed in all patients scheduled for CABG when the use of a radial artery and/or saphenous vein is planned. In particular, endoscopic RA harvesting is feasible in every patient following the confirmation of a negative Allen's test (especially with the use of pulse oximetry) typically from the non-dominant arm. However, even the dominant arm can be considered in selected instances (recent radial angiography or positive Allen's test from the non-dominant arm).

A careful selection of such candidates could be helpful during the initial phase of the adoption of endoscopic approaches in order to avoid unnecessary disappointment and frustration for the team involved. In general, obese patients should be avoided during the steep phase of the learning curve especially when the operator has no experience with an endoscopic approach and limited support is available.

Surgical Technique

Surgical Equipment

As outlined above, an endoscopic surgical approach with a non-sealed system is described in detail.

In particular, the following armamentarium can be used both for RA and SV procurement:

- Endoscopic re-usable retractor (Bisleri Model, Karl Storz, Tuttlingen, Germany), which is equipped with a 5 mm forward-oblique 45° telescope;
- Impedance-controlled bipolar radiofrequency vessel sealing system (LigaSure Maryland, Medtronic, Minneapolis, MN, USA);
- Left and right curved pigtail vessel dissector (Hook Ring Dissector, Karl Storz, Tuttlingen, Germany).

Endoscopic Radial Artery Harvesting

The arm is prepped, draped and placed on an arm board perpendicular to the long axis of the operating table. Avoidance of excessive extension at the level of the shoulder is recommended in order to avoid neurological injury to the brachial plexus. In order to provide an adequate setting for endoscopic RA harvesting, the arm needs to be secured to the arm board and a rolled towel is typically placed below the wrist allowing for hyperextension of the hand (Fig. 14.1), which is crucial to achieve a proper exposure. Of note, this endoscopic approach (unlike the sealed system) does not require the use of a tourniquet around the arm: thus, an important anatomical landmark such as the pulsation of the radial artery can represent an essential advantage especially in difficult cases.

First Step: Exposure of the Radial Artery

A longitudinal incision (2–2.5 cm) is performed at the level of the volar surface of the forearm beginning 1 cm proximal to the radial styloid prominence. First, the RA is identified and the dissection is started as a pedicle: it is recommended to avoid the use of hemoclips for side branch or tissue division (the vessel sealing system is used instead) as they could become dislodged by the retractor during endoscopic harvesting maneuvers (Fig. 14.2).

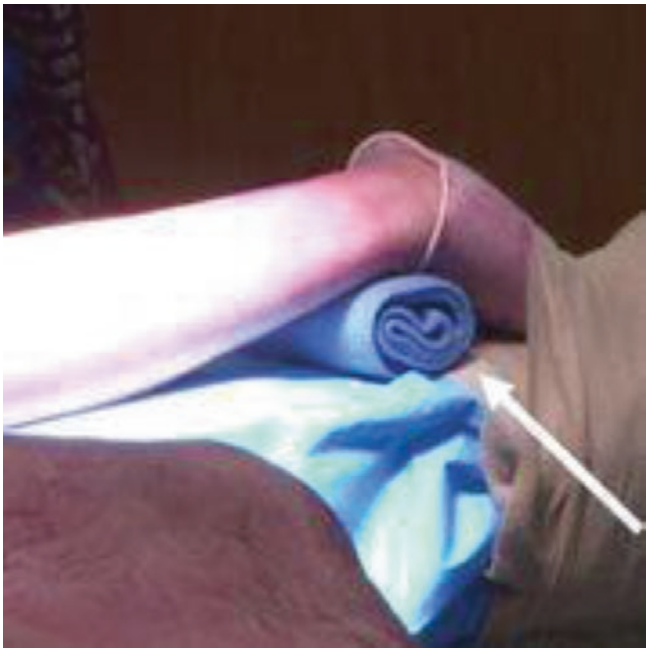

Fig. 14.1 Arrow depicts the rolled towel placed below the wrist to achieve hyperextension. Arm is also secured to the arm board

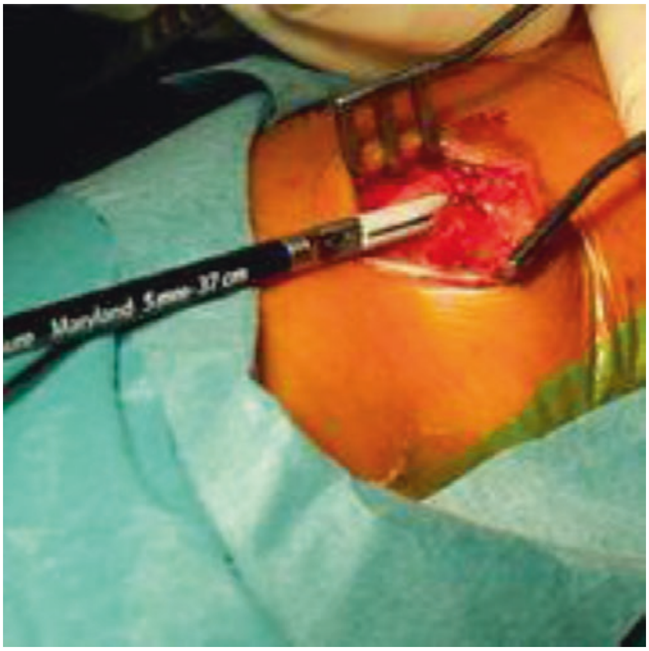

Fig. 14.2 Identification and isolation of the radial artery under direct vision

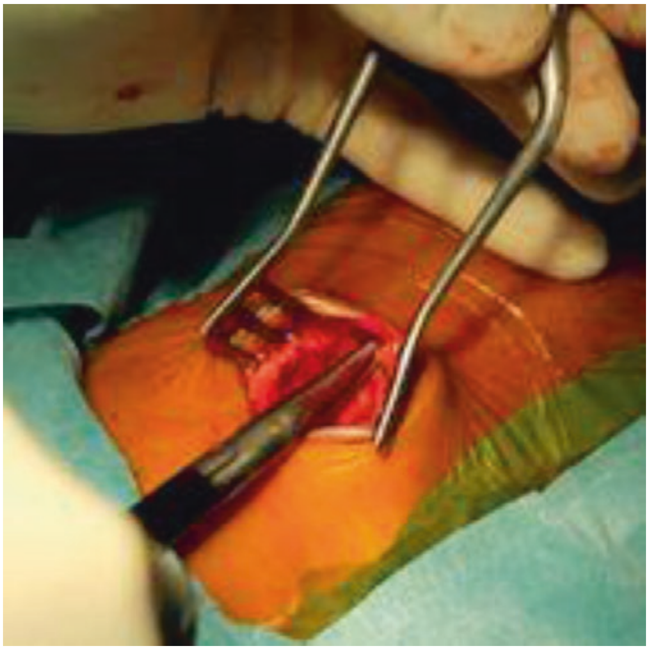

Fig. 14.3 Self-retaining retractor is gently lifted in order to improve exposure and allow isolation under direct vision

The initial goal is to achieve a full mobilization of the RA as a pedicled graft with the vessel sealing system under direct vision. Side branches are divided by means of impedance-controlled bipolar radiofrequency vessel sealing system (LigaSure Maryland, Medtronic, Minneapolis, MN, USA). Such dissection should be extended proximally (towards the antecubital fossa) as much as possible under direct vision by lifting the self-staying retractor (Fig. 14.3).

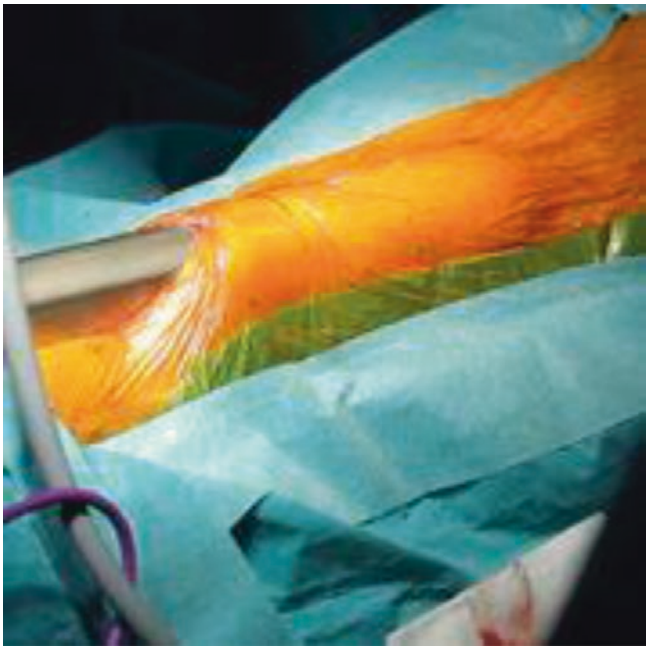

Fig. 14.4 Insertion of the dedicated endoscopic retractor

Care is taken to separate the RA from the superficial radial nerve, which is the only one of the two nerves (the other one being the lateral antebrachial cutaneous nerve) that can be damaged during endoscopic RA harvesting. In fact, the endoscopic approach avoids completely the risk of damage to the lateral antebrachial cutaneous nerve, thereby reducing the incidence of postoperative neurological complications.

Once a length of at least 3–4 cm is harvested under direct visualization, a specifically designed reusable endoscopic retractor (Karl Storz, Tuttlingen, Germany) can be inserted and used for mechanical retraction (Fig. 14.4).

Second Step: Endoscopic Harvesting

The first endoscopic step is aimed at dividing the fascia between the brachioradialis and flexor carpi muscle until the antecubital fossa is reached. It is important to maintain a dissection plane just limited to the fascia itself (even if the course of the RA tends to be beneath the brachioradialis muscle) and avoid the division of any muscular structure in order to minimize the risk of bleeding and hematoma (Fig. 14.5).

Once the fascia has been opened, the division of side branches and tissue on the brachioradialis side of the RA is performed first (Fig. 14.6): in most instances, the course of the RA (beneath the brachioradialis muscle) may provide inadequate exposure. The division of the tissue/side branches only on the brachioradialis side (while the flexor carpi side is transiently maintained intact) can 'pull' the RA

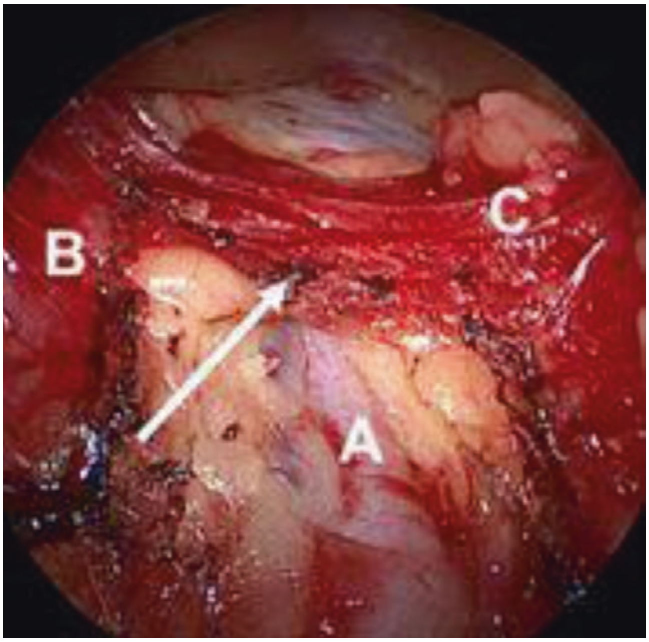

Fig. 14.5 Dissection of fascia (arrow) to expose the radial artery (A) between the flexor carpi (B) and the brachioradialis muscle (C)

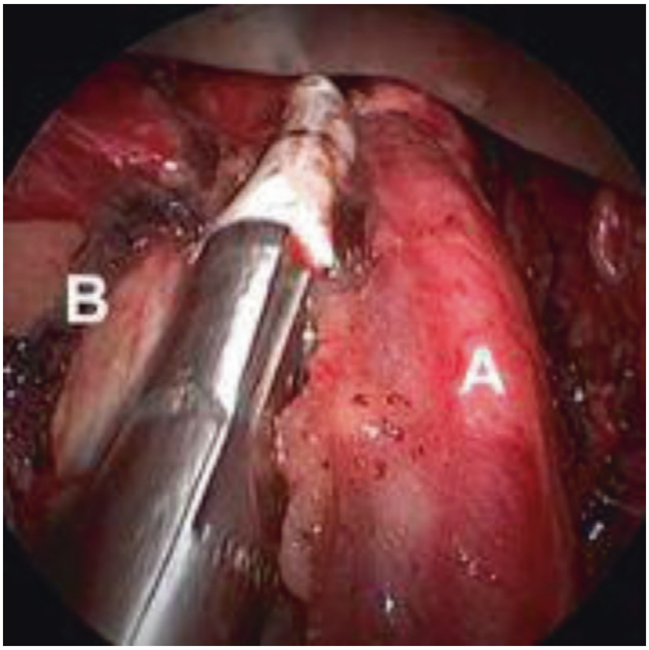

Fig. 14.7 Dissection of radial artery (A) from surrounding tissues and side branches from the flexor carpi muscle (B) side

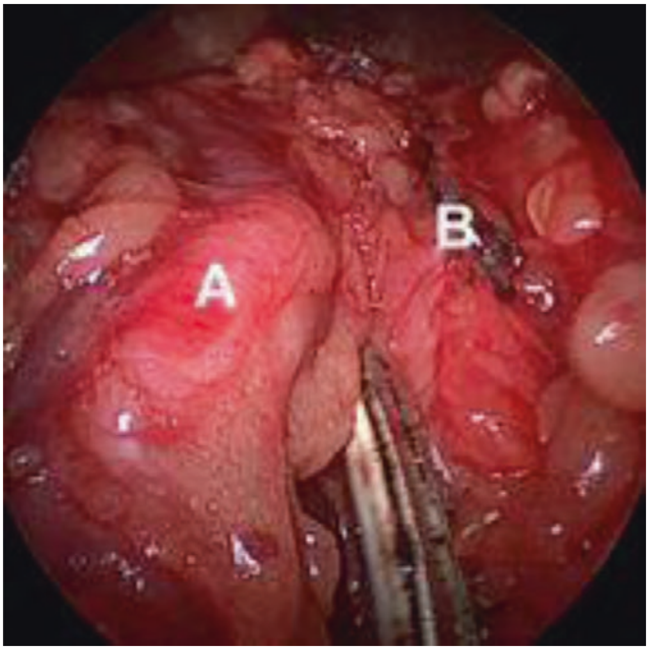

Fig. 14.6 Dissection of radial artery (A) from surrounding tissues and side branches at first from the brachioradialis muscle (B) side

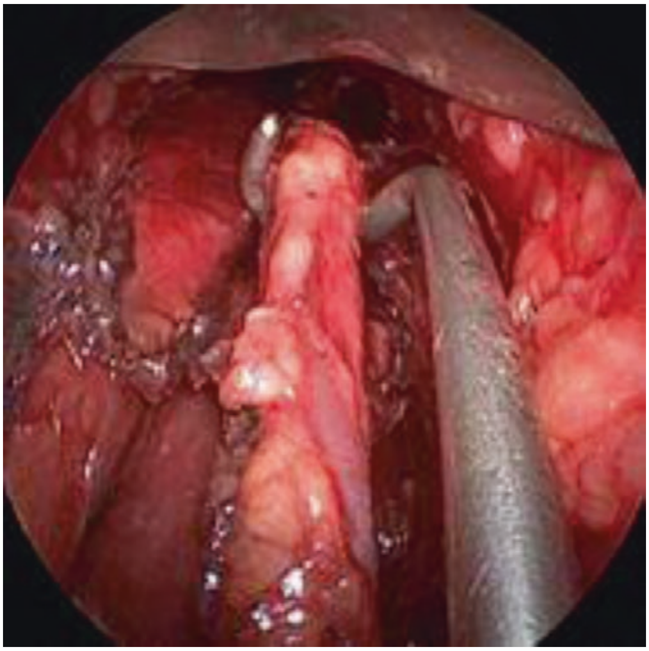

Fig. 14.8 Confirmation of the absence of residual side branches or tissue by means of pigtail vessel dissector

towards the midline and significantly improve the endoscopic exposure. In some instance, this phase may require retractor to be gently used to lift the brachioradialis muscle itself.

Then, the flexor carpi side of the RA is dissected as proximal as to the antecubital fossa just by using the vessel sealing system as well (Fig. 14.7). Any residual side branch on the inferior aspect is also divided, if required. The absence of any residual side branches is finally confirmed by means of pigtail vessel dissector (Hook, Karl Storz) (Fig. 14.8).

At any stage, bleeding may occur due to inadvertent injury to a side branch: in such instance we recommend to pull out all the equipment and perform a gentle compression; unless a major damage has occurred at the level of the RA, such maneuver is usually effective to achieve hemostasis.

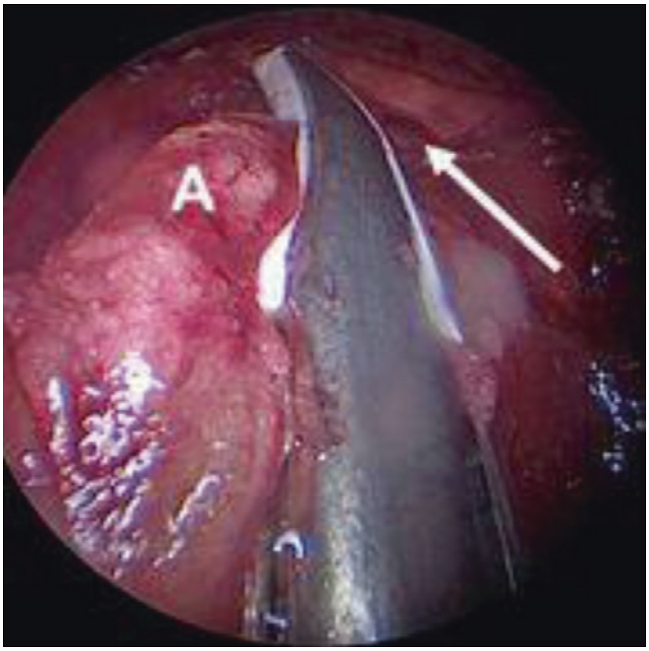

Fig. 14.9 Single incision technique: radial artery is endoscopically divided proximally (antecubital fossa) by means of vessel sealing system (arrow) passing across the radial artery (A)

Final Step: Radial Artery Retrieval

Once the RA harvest is complete and no residual side branches can be identified by means of the pigtail vessel dissector, the full length of the conduit can be retrieved in two different ways:

- Single incision approach: the vessel sealing system is used to divide the radial artery endoscopically at the level of antecubital fossa (proximal) and then the conduit is retrieved via the same distal starting incision at the level of the wrist (Fig. 14.9).
- Counter incision approach: a second incision (2 cm long) is performed near the antecubital fossa. A blunt dissection is performed under endoscopic control using the tip of the dissector as a landmark and a tape is then passed around the radial artery, which can be divided at the level of the wrist and pulled out from the proximal (towards the antecubital fossa) incision (Fig. 14.10).

Endoscopic Saphenous Vein Harvesting

It is highly recommended to map the course of the vein by means of ultrasound especially at the level of the thigh; this maneuver is critical to precisely locate the site of the initial incision as well as to identify any possible anatomical variation. Furthermore, it is advisable to transiently place a tourniquet at the thigh to further improve vein mapping (Fig. 14.11).

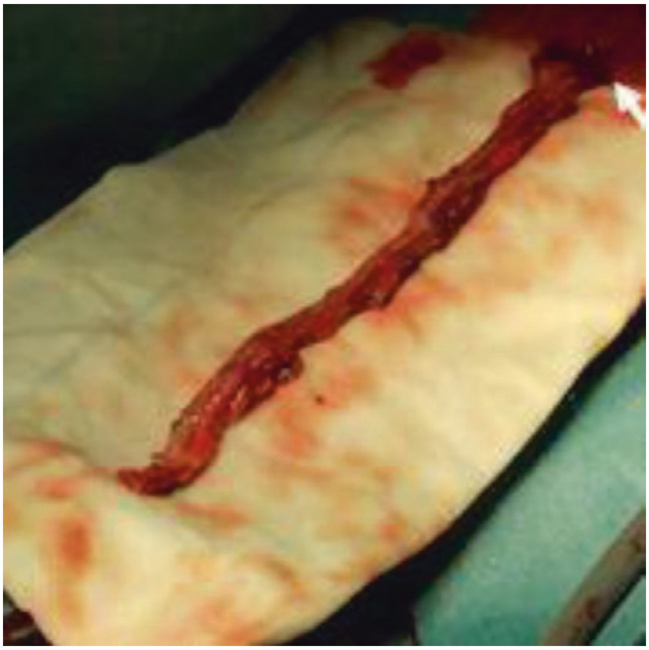

Fig. 14.10 Counter incision technique: the harvested radial artery is retrieved through a second counter incision (white arrow) at the level of the antecubital fossa

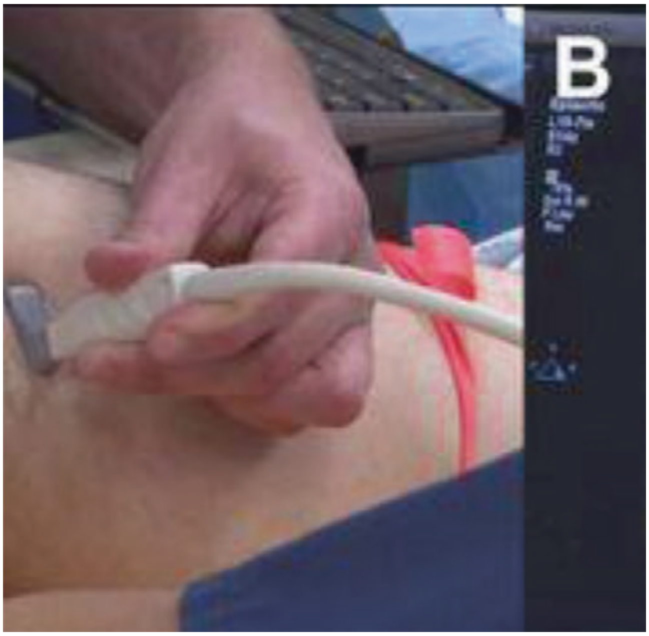

Fig. 14.11 Mapping the course of the saphenous vein by means of ultrasound above the knee

Patient is positioned with the legs slightly bent with a rolled sheet placed under the knees, thus achieving a “frog like” position in order to better expose the course of the great saphenous vein.

First Step: Exposure of the Great Saphenous Vein

A small 2–3 cm longitudinal incision is made above the knee and by means of self-staying retractor, subcutaneous tissue is divided in order to reach and fully mobilize the first 3–4 cm of the saphenous vein. A vessel loop is then passed around the vein to achieve counter traction during harvesting maneuvers (Fig. 14.12). Next, gentle dissection of all the surrounding tissues and side branches is performed by means of impedance-controlled bipolar radiofrequency vessel sealing system (LigaSure Maryland, Medtronic, Minneapolis, MN, USA) as far as possible under direct visualization by lifting the self-retaining retractor. This maneuver is critical to ensure enough space for the insertion of the dedicated reusable stainless steel endoscopic retractor (Bisleri Model, Karl Storz, Tuttlingen, Germany). Similar to RA harvesting, the use of hemoclips is not necessary also during the initial phases of saphenous vein procurement.

Second Step: Endoscopic Harvesting

In general, it is recommended to initiate the endoscopic harvesting above the knee and to proceed towards the groin (Fig. 14.13). A full length harvesting of the vein at the level of the thigh can usually provide a segment in the range of 20–25 cm. In case an extra-length is required, the endoscopic harvesting can be continued via the same incision but towards the knee and beyond (Fig. 14.14). It is also possible to perform an additional incision beneath the knee towards the ankle if additional segments of vein are required.

Endoscopic dissection of the tissue (surrounding the vein) as well as side branches is then performed by gently advancing the dedicated endoscopic retractor and the vessel sealing system only (Fig. 14.15).

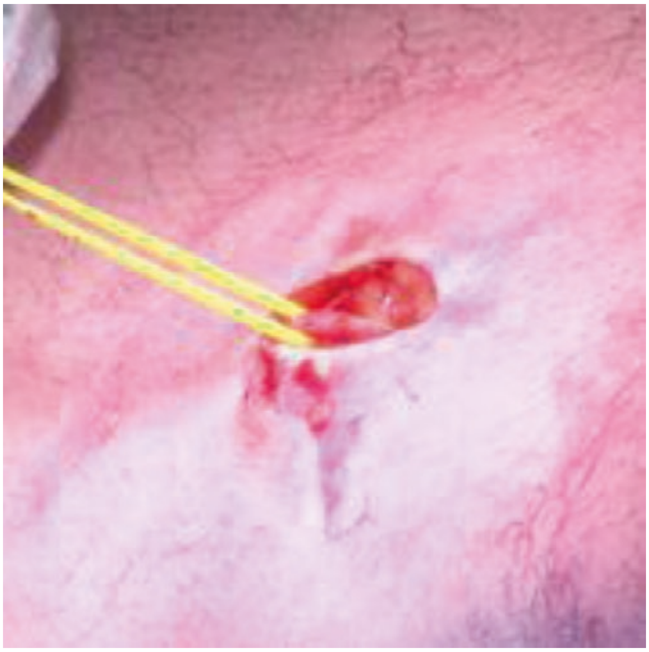

Fig. 14.12 Vessel loop around the saphenous vein after initial isolation at the level of the knee

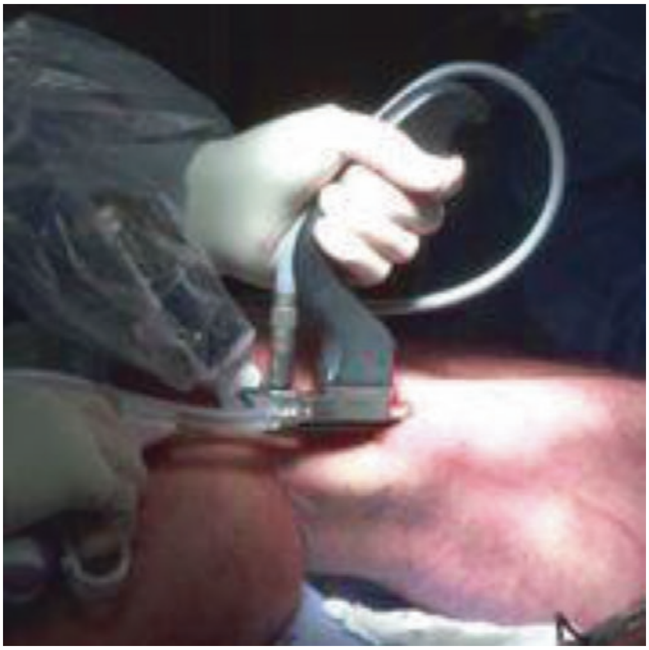

Fig. 14.13 Saphenous vein harvesting is started above the knee and continued towards the groin

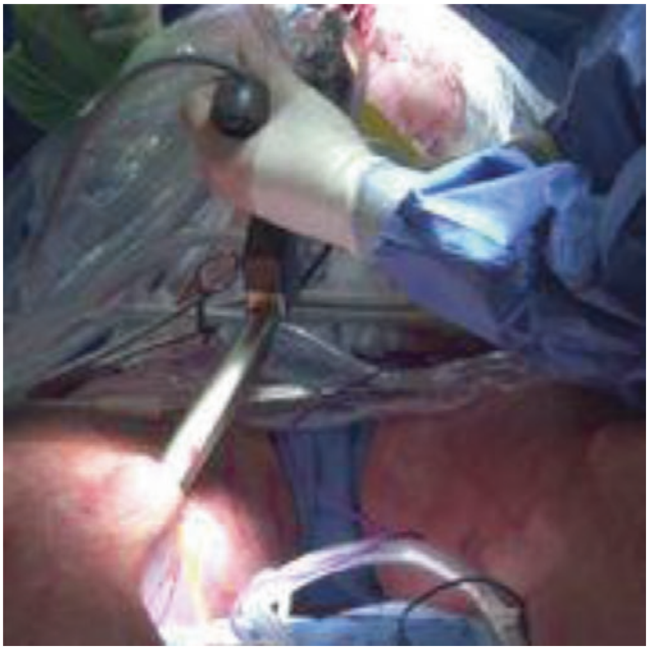

Fig. 14.14 Endoscopic harvesting continued via the same starting incision and proceeding towards the knee and beyond in case an extra-length is required

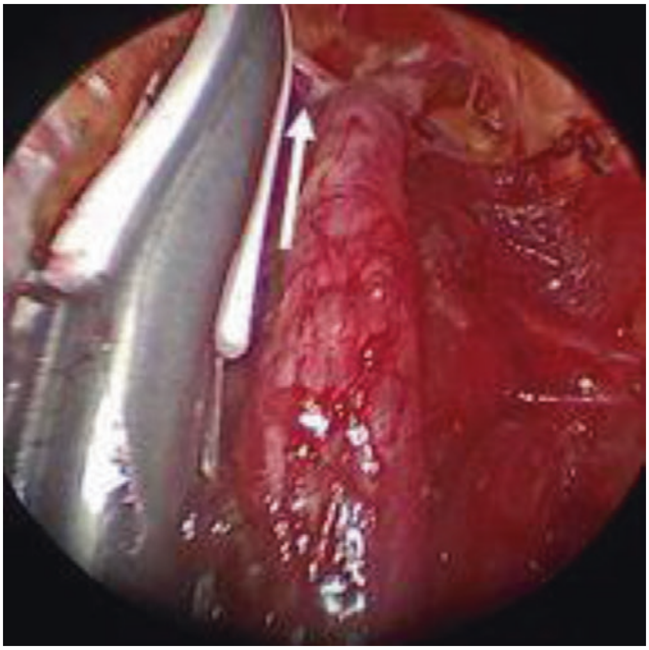

Fig. 14.15 Endoscopic dissection of the saphenous vein from the surrounding tissue. Arrow highlights a side branch during the sealing phase

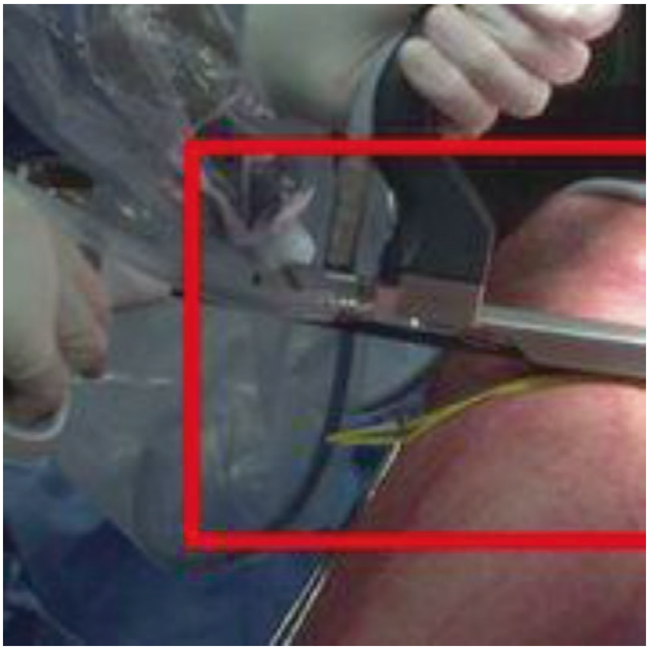

Fig. 14.16 Red box highlights vessel loop used as counter traction during saphenous vein harvesting

Unlike the RA, there is not a pre-determined sequence of layers division; instead, each case must be adapted to the specific patient's characteristics and in general should follow the rationale of dissecting the vein at first on the side where a more relevant traction (by subcutaneous tissue or side branches) is noted. It is also recommended to maintain an effective counter traction throughout the endoscopic procedure by using a vessel loop around the segment of the vein which has been initially exposed under direct vision (Fig. 14.16). Finally, it should be noted that this approach allows for a "pedicled" harvesting technique of the saphenous vein: the maintenance of surrounding tissue around the vein has recently been associated with improved long-term patency rates and clinical outcomes although preservation of such tissue has been described only with an open approach [41]. Further studies are obviously warranted to elucidate this aspect in an endoscopic fashion.

As it may occur during endoscopic RA harvesting, any inadvertent injury of small side branches may result in bleeding that appears more significant than normal because of the magnification by the endoscopic view. It is therefore recommended to pull out the endoscopic retractor and the vessel sealing system and to perform a gentle compression for several minutes as described before.

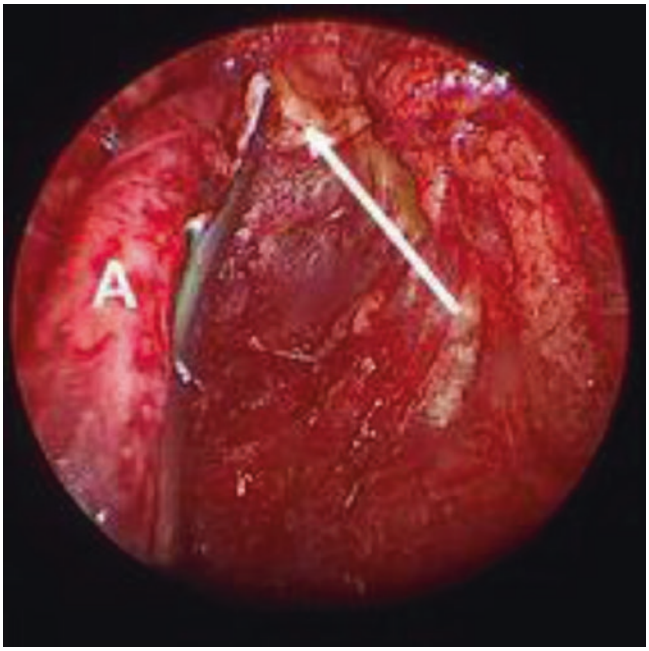

Fig. 14.17 Single incision saphenous vein retrieval: the vessel sealing system is passed across the graft and the vessel is divided endoscopically (A: vein graft; white arrow: proximal saphenous vein at the level of the groin)

Final Step: Saphenous Vein Retrieval

Once harvesting is completed, it is recommended to verify the absence of residual tributary branches by means of the pigtail vessel dissector (Hook, Karl Storz, Tuttlingen, Germany). Similar to the RA procurement, the SV can be retrieved by using a single or double incision for proximal ligation (Fig. 14.17).

Conclusion

During the past decade, increasing evidence supporting the safety and efficacy of endoscopic SV and RA harvesting has emerged. These techniques can be reliably used not only as alternative to the open approach but actually as standard of care in patients undergoing CABG. The development of novel tools for endoscopic vessel harvesting can further popularize these techniques. In particular, the adoption of a non-sealed approach seems to be associated with a lower risk of damage to the conduit. However, further investigations are warranted to firmly establish these findings.

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Conventional Coronary Artery Bypass Grafting

15

Kirthi Ravichandren and Faisal G. Bakaeen

High Yield Facts

- Conventional coronary artery bypass grafting (CABG) on cardiopulmonary bypass (CPB) is the gold standard for treatment of coronary artery disease.
- The use of CPB and cardioplegic arrest allows optimization of the surgical field and consistent placement of grafts.
- Single clamp is preferred to side clamp technique during proximal anastomosis to reduce atheroemboli.
- In most modern series the observed mortality risk in CABG is 1–3%.
- According to the STS database the major complications include stroke (1.3%), renal dysfunction (2.1%), deep sternal wound infection (0.3%) and atrial fibrillation (24%).
- Patients undergoing CABG must receive 81–325 mg of aspirin indefinitely postoperatively.
- In CABG after acute coronary syndromes, consider restarting dual antiplatelet therapy for 6 months when bleeding risk is diminished.

Introduction

Conventional coronary artery bypass grafting (CABG), the gold standard for myocardial surgical revascularization includes the use of cardiopulmonary bypass (CPB) with cardiac arrest for construction of vascular anastomoses to the coronary arteries without cardiac motion or hemodynamic compromise. In USA approximately 85% of CABG is performed using CPB. The chief goal of CABG is to increase symptom free survival in patients with severe coronary artery disease (CAD) using a surgical approach that fits the patients anatomic and physiologic risk profile [1].

History of Coronary Artery Bypass Surgery

Over the years innovation, meticulous research and implementation has made surgical myocardial revascularization safe, effective and most durable technique [2]. The key historical contributions behind this most commonly performed cardiac surgical procedure are summarized in Table 15.1.

Table 15.1 An overview of history of CABG

1950	A. Vineberg	Direct implantation of mammary artery into myocardium
1953	J. H. Gibbon	First successful use of CPB machine
1962	F. M. Sones	Successful selective cine angiography
1962	David Sabiston, Jr	First reported successful CABG
1964	T. Sondergaard	Introduced routine use of cardioplegia for myocardial protection
1964	D. A. Cooley	Routine use of normothermic arrest for all cardiac cases
1968	R. Favaloro	First large series showing success of CABG
1973	V. Subramanian	First on-pump CABG

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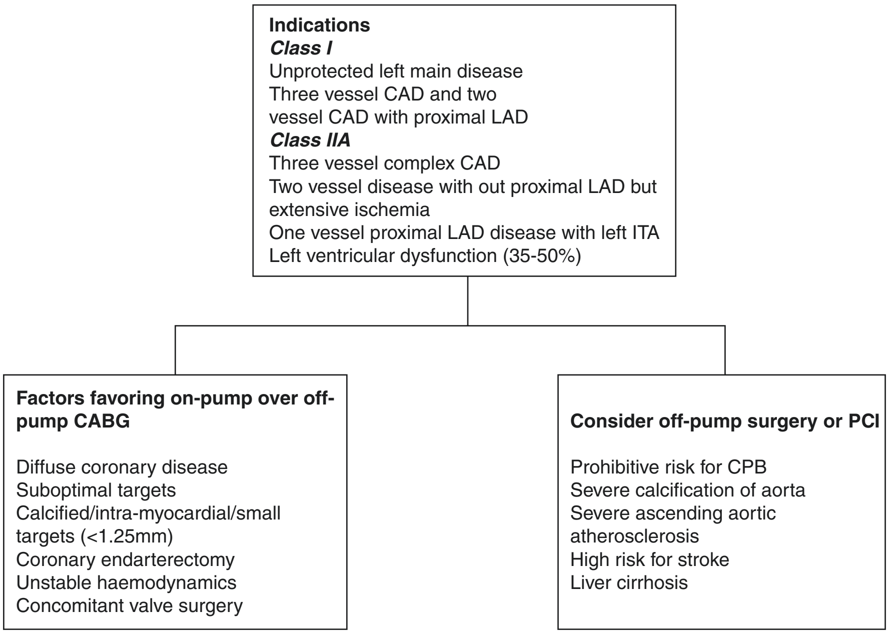

Indications
Class I
Unprotected left main disease
Three vessel CAD and two vessel CAD with proximal LAD
Class IIA
Three vessel complex CAD
Two vessel disease with out proximal LAD but extensive ischemia
One vessel proximal LAD disease with left ITA
Left ventricular dysfunction (35-50%)
Factors favoring on-pump over off-pump CABG
Diffuse coronary disease
Suboptimal targets
Calcified/intra-myocardial/small targets (<1.25mm)
Coronary endarterectomy
Unstable haemodynamics
Concomitant valve surgery
Consider off-pump surgery or PCI
Prohibitive risk for CPB
Severe calcification of aorta
Severe ascending aortic atherosclerosis
High risk for stroke
Liver cirrhosis

Fig. 15.1 Patient selection algorithm for coronary artery bypass grafting. *CABG* coronary artery bypass grafting, *CAD* coronary artery disease, *CPB* cardiopulmonary bypass, *LAD* left anterior descending artery, *ITA* internal thoracic artery (Produced by, Cleveland Clinic Center for Medical Art & Photography)

Indications for CABG

We have designed a simplified algorithm for patient management and intervention strategy selection based on extent of CAD and patient risk profile (Fig. 15.1) [3].

Conduct of the Operation (Table 15.2)

Table 15.2 Key technical steps in conventional CABG

• Stop the ventilation and pull the saw upwards during sternotomy to prevent injury to underlying structures, although not a significant risk in primary CABG
• Avoid high mean arterial pressure during sternotomy and aortic cannulation
• Maintain higher perfusion in patients with high risk for CVA and in older patients
• If the target vessel is small, use a vessel probe (1 mm) inside the coronary artery lumen to avoid suturing the back wall and narrowing the vessel
• Use of CO_2 blower to enhance visualization during anastomosis
• It is important to make a smaller coronary arteriotomy when performing a side-to-side anastomosis
• De-air in situ ITA grafts before tying the sutures to prevent air embolism
• Single clamp is preferred to side clamp technique during proximal anastomosis to reduce atheroemboli
• Protamine adverse reaction can range from transient hypotension to fatal anaphylaxis
• In situations of difficulty achieving hemostasis, assess for the platelet dysfunction, coagulopathy and hypothermia
• Place the chest tubes below the rectus fascia to avoid herniation
• Excessively tight approximation of sternum with excess tension can result in malperfusion of the bone increasing the risk of wound infection

Incision

Sternotomy is the standard incision for CABG. The patient lies in a supine position with the arms secured at his side. The median vertical incision from sternal notch to the tip of the xiphoid is made. Then the midline is identified and the sternal osteotomy is performed with an electric or air-powered saw. The bleeding is controlled by sealing the bone marrow with towels, antibiotic paste or bone wax. The sternum is retracted slowly and progressively with dedicated retractor.

Division of the Pericardium

The pericardium is opened and a cradle is created using retraction sutures to enhance exposure.

Cannulation

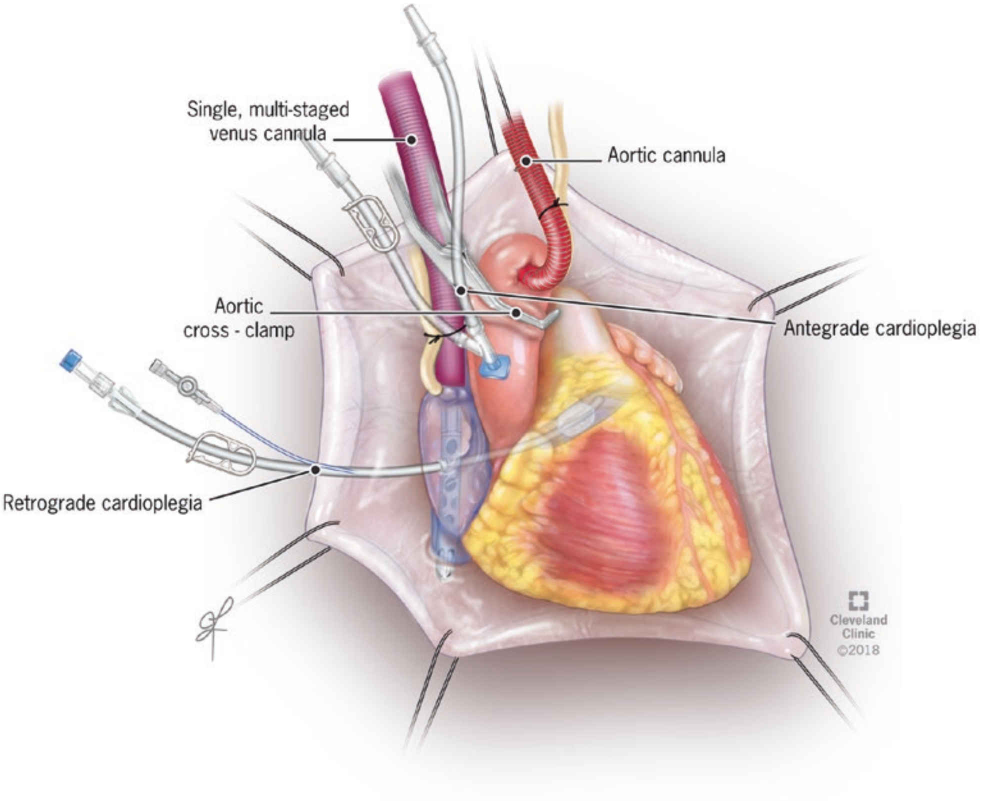
Aortic

Two purse strings running through the aortic media are placed on the aorta at opposite ends. The incision is made in disease free segment of the ascending aorta, slightly smaller than the diameter of the aortic cannula. The cannula is advanced atraumatically and secured. In patients with severe atherosclerotic disease in aorta, an epiaortic ultrasound is necessary to identify safe site for cannulation and aortic cross clamp (Fig. 15.2).

Venous

The cannulation can be done in dual stage, with purse strings placed in the right atrium (Fig. 15.2). A 2-cm vertical inci-

Fig. 15.2 Conduits used in CABG (Produced by, Cleveland Clinic Center for Medical Art & Photography)


Single, multi-staged
venus cannula
Aortic cannula
Aortic
cross - clamp
Antegrade cardioplegia
Retrograde cardioplegia
Cleveland
Clinic
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sion is made in the right atrium and is dilated before inserting the cannula. Some dual stage cannula may need to be supplemented with an SVC cannula if the venous drainage needs to be improved.

Initiation of Cardiopulmonary Bypass

Once retrograde and antegrade cannulae for cardioplegia have been placed the CPB is initiated. Aorta is cross clamped and an induction dose of antegrade and retrograde cardioplegia (700–1000 mL) is administered to achieve diastolic myocardial arrest. Induction dosing and maintenance dosing depends on type of cardioplegia used [4]. Typically normothermia is preferred and hypothermia is reserved for patients having issues with myocardial protection.

Target Identification and Preparation

The conduits are chosen at the beginning of the surgery, harvested before giving heparin (Fig. 15.3) and are prepared for anastomoses (Fig. 15.4). The targets are identified by placing wet sponges behind the heart and by lifting the heart atraumatically. The pericardium is pulled up on the left or right side to enhance exposure of the coronary arteries.

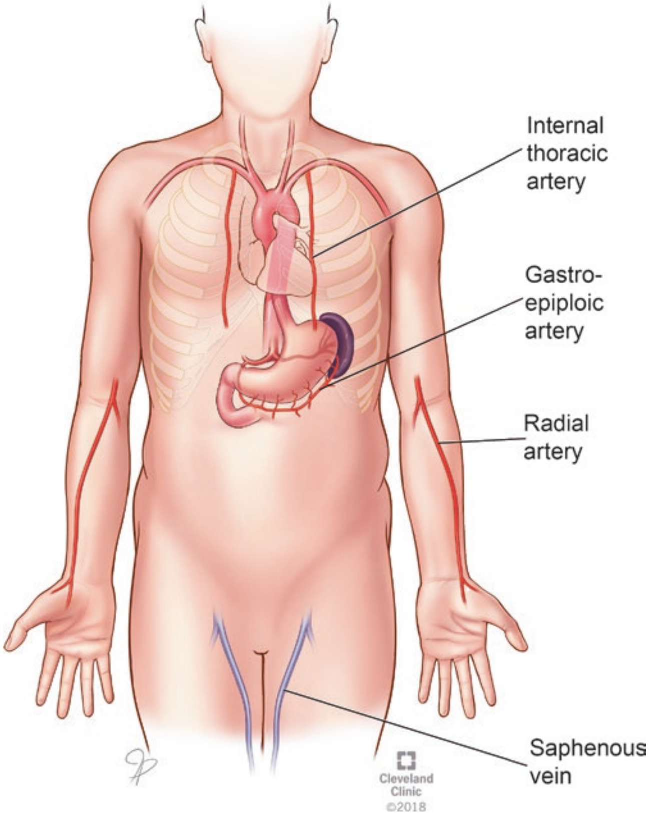
Internal
thoracic
artery
Gastro-
epiploic
artery
Radial
artery
Saphenous
vein
Cleveland
Clinic
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Fig. 15.3 Intracardiac and vascular cannulae used for CPB (Produced by, Cleveland Clinic Center for Medical Art & Photography)

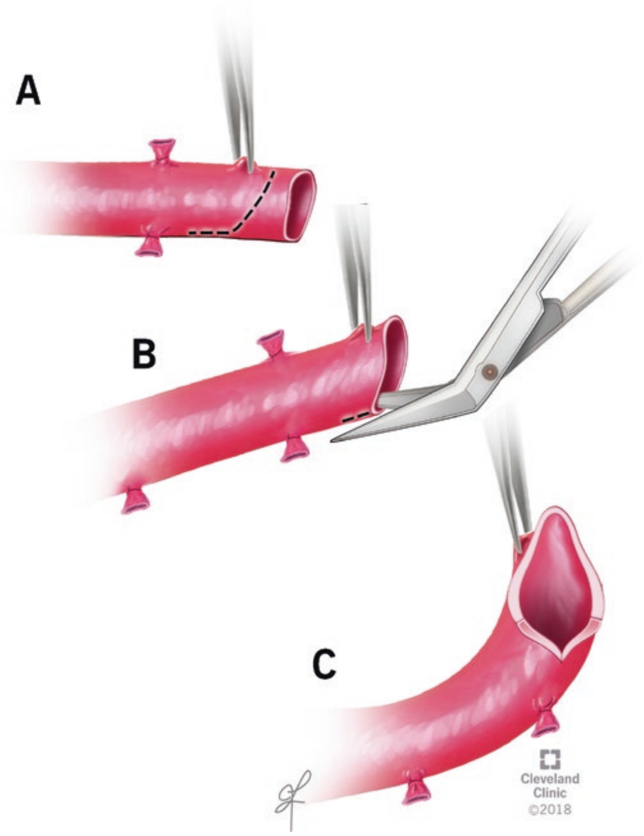


Fig. 15.4 Conduit preparation. (**a**) Bevel the edge of the conduit. (**b**) Cut back to create notch at the heel. (**c**) Heel and toe of the conduit (Produced by, Cleveland Clinic Center for Medical Art & Photography)

Arteriotomy

Visualization with optical magnifier (×2.5–3.5) is necessary for precision. Fat tissue around the coronaries can be trimmed or held away with a retractor or 5/0 suture to expose the location for distal anastamosis. The lumen of coronary artery is entered by gently stroking on the surface with the belly of a No.15 blade. The arteriotomy is enlarged with fine coronary artery scissors approximately to match the size of the conduits.

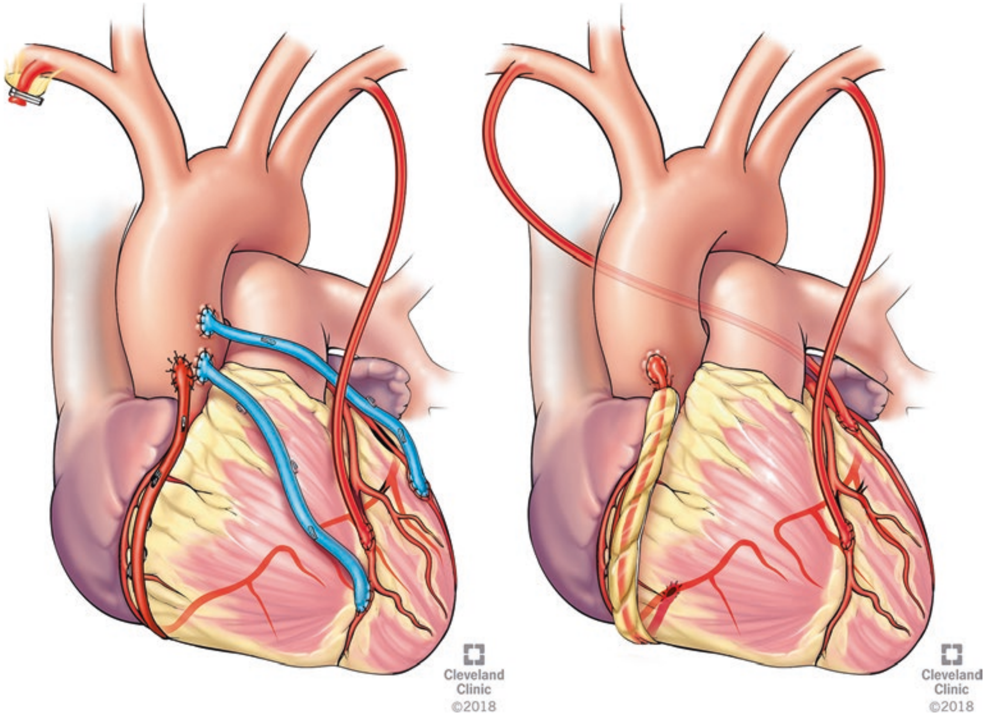
Distal Anastomoses

Bevel the edge of saphenous vein graft (SVG) and make the end-to-side anastomosis with running fine suture using 7/0 (8/0 polypropylene is used when the target vessel is small or friable).

Graft Configurations

Composite grafts such as sequential or Y-graft can be performed using end-to-side and side-to-side anastomoses. A common surgical approach for arterial grafting of circumflex coronary artery is to tunnel the in-situ right ITA through transverse sinus (Figs. 15.5 and 15.6). The most common grafting strategy in the North America is left internal thoracic artery (LITA) to left anterior descending coronary artery (LAD) and veins to the other targets.

Fig. 15.5 Graft configuration with different conduits. (Left) Bilateral ITA with free right ITA and two saphenous vein grafts. (Right) In-situ right ITA passing through transverse sinus and radial artery graft to an occluded or greater than 90% stenosis (Produced by, Cleveland Clinic Center for Medical Art & Photography)



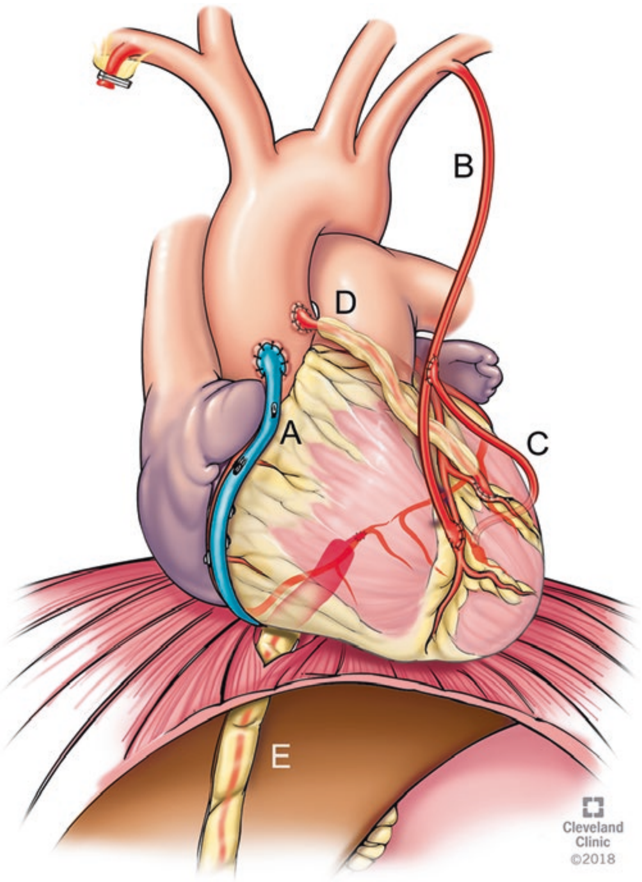


Fig. 15.6 Graft configuration with different conduits. (**a**) Saphenous vein graft. (**b**) In-situ left ITA. (**c**) Free right ITA as Y-graft. (**d**) Radial artery graft. (**e**) Gastroepiploic artery graft (Produced by, Cleveland Clinic Center for Medical Art & Photography)

There is growing evidence of benefit from multi arterial grafting (with right ITA or radial artery in addition to gold standard LITA-LAD graft) [5, 6]. The interim results of the ART trial showed no difference in mortality between patients receiving single or bilateral ITA and the 10-year results are heavily anticipated for later this year [7].

Proximal Anastomoses

The coronary grafts are placed anteriorly or on the lateral sides of the aorta. The proximal anastomoses can be constructed as T or Y graft to the in-situ LITA or proximal end of other completed grafts in severe atherosclerosis of the aorta.

De-Airing and Cross Clamp Removal

Routine de-airing, before and after cross clamp removal, is performed to avoid air embolism. This is achieved by needle de-airing of individual grafts and the venting of the aortic root with passive ventricular filling by partially clamping the venous line and with a valsalva maneuver on the ventilator while simultaneous monitoring of the air removal with transesophageal echocardiogram (TEE).

Additional maneuvers such as positioning the patient in Trendelenberg tilt, shaking the heart or placing a needle in the left ventricle can be used. Then remove the aortic clamp after reperfusing the myocardium with warm cardioplegia (300–400 mL).

Decannulation

Resume ventilation and wean from CPB after:

- Resumption of sinus rhythm with adequate heart rate and place temporary pacing wires.
- Rewarming to physiologic core body temperature.
- Correction of hematocrit, potassium, glucose and arterial blood gas.
- Assessing systolic function and ruling out new wall motion abnormalities using TEE.

Then the venous and arterial cannulae are removed and protamine is administered.

Sternal Closure

Coagulopathy should be promptly corrected during rewarming and chest tubes are placed. Four to eight stainless steel wires are used singularly or in figure of eight fashion passing perpendicularly through the intercostal space. The retrosternal side of the wire is examined for bleeding and hemostasis is achieved. Wires are twisted and cut after tightly approximating the sternal halves. Following this subcutaneous tissue and skin is closed. It is best to avoid transfusion unless clinically indicated.

Outcomes

Hospital Mortality

Working Group panel on the cooperative CABG database project suggests that seven core variables including age, gender, acuity of operation, left ventricular function, previous operation, left-main coronary artery disease and number of diseased coronary arteries (70%) are unequivocally prognostic of 30-day and in-hospital mortality after CABG [8].

With STS database being the largest voluntary national database, risk calculators predict expected mortality for a given patient (risk characteristics) and the risk-adjusted outcomes have become the gold standard quality measurement for CABG. In most modern series the observed mortality risk in CABG is 1–3%.

Table 15.3 Important morbidity associated with CABG

Complication	Incidence	Risk factor	Recommendation/Prevention/Treatment
Stroke	1.3%	Advanced age, history of stroke, diabetes mellitus (DM), hypertension, female sex and, preoperative atherosclerotic disease (radiographic evidence of previous stroke or aortic atheromatous disease)	Carotid duplex scanning for high risk patients with or without previous cerebrovascular accident (CVA) to consider carotid revascularization along with CABG
Delirium	<10%	Advanced age, preexisting cognitive impairment, vascular disease	Supportive management Few studies have related it to functional decline at 1 month, short term cognitive decline, and risk of late mortality
Cognitive impairment	Varies	Preexisting CVA or cognitive impairment	**Short term** Generally mild in most patients and resolve within 3 months postoperatively **Long term** No difference between late cognitive outcomes with or without CPB
Mediastinitis	Superficial Deep 0.3%	DM, body mass index >30 kg/m, chronic obstructive pulmonary disease (COPD), reoperation, prolonged intubation time, surgical re-exploration	***Prevention*** Preoperative screening and decolonization of methicillin resistant *Staph auereus*, single dose antibiotic prophylaxis, topical antiseptic cleanser, proper hair removal with electric clipper than razors, adequate preoperative glycemic status and weight loss Operative Sterile technique, minimizing electro-cautery and bone wax, double-gloving, shorter operative times ***Treatment*** Surgical debridement with reconstruction with pectoral muscle flap, vacuum assisted closure bridged to flap advancement with sternal osteosynthesis
Renal dysfunction	2.1%; 1% need dialysis	Preoperative renal dysfunction, peripheral arterial disease (PAD), advanced age, preoperative Intraortic balloon pump (IABP), LV dysfunction, CHF, shock, emergency CABG	***Prevention*** Maintain perioperative hematocrit >19% and mean arterial pressure >60 mmHg, in case of preoperative renal dysfunction, off-pump CABG, N-acetylcysteine, delay CABG until recovery from contrast induced nephropathy which is self-limiting (3–5 days)
Myocardial dysfunction (Type V MI)	NA	LV dysfunction, left main CAD	***Prevention*** Use of IABP in absence of aorto-illiac occlusive disease or PAD, aggressive attempts at blood conservation to avoid allogeneic red blood cell transfusion
Postoperative atrial fibrillation (AF)	24%	Advanced age, male, COPD, concomitant valvular heart disease, left atrial enlargement, pre-CABG AF, pericarditis, reoperation	***Prevention*** Preoperative and postoperative beta blocker is highly effective. Patients with pre-CABG AF, post-CABG AF resolves spontaneously within 6 weeks and requires ventricular rate control until then. Anticoagulation is recommended in patients with AF with risk of thromboembolism

CABG coronary artery bypass grafting, *CHF* congestive heart failure, *LV* left ventricular, *NA* not available

Table 15.4 Perioperative antiplatelet therapy in patients undergoing CABG

Class	Class I	Class IIa (with extensive ischemia)
Preoperative	1. Administer 81–325 mg of aspirin to patients undergoing CABG 2. For non-urgent CABG, stop clopidogrel and ticagralor for >5 days, and prasugrel >7 days to reduce blood transfusion 3. In urgent CABG, discontinue clopidogrel and ticagrelor for at least 24 h, eptifibatide and tirofiban for at least 2–4 h and abciximab for at least 12 h, to reduce major bleeding complications	Discontinue aspirin 3–5 days preop for patients with increased risk of bleeding or those who refuse blood transfusion
Postoperative	Administer 81–325 mg of aspirin to CABG patients indefinitely In CABG after acute coronary syndromes, consider restarting dual antiplatelet therapy for 6 months when bleeding risk is diminished	

Hospital Morbidity

A detailed analysis of risk-adjusted outcomes from national STS database for CABG is tabulated (Table 15.3) [3, 9].

Antiplatelet Therapy

The efficient practice for antiplatelet therapy in patients with CAD before and after CABG from the updated AHA (2014) and STS (2012) guidelines is depicted in Table 15.4.

Conclusion

Success after CABG greatly depends on graft patency and secondary prevention of coronary artery disease progression. A heart team approach on aggressive medical therapy, lifestyle modification and cardiac rehabilitation is essential [3]. The best method to ensure long-term patient adherence to treatment is education on disease control as part of comprehensive secondary prevention approach before discharge.

Although surgical research in the pathophysiology of graft patency has increased, understanding of various graft function is ongoing. Undeterred by the challenges of changing healthcare and growing technology, conventional CABG has inimitably proven its clinical effectiveness for the treatment of CAD to this day.

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Additional Resources

Online

CTSNet; https://www.ctsnet.org/videos

Online STS Adult Risk Calculator. http://riskcalc.sts.org/stswebriskcalc/#/calculate

STS Clinical Practice. https://www.sts.org/resources/clinical-practice-credentialing-and-reporting-guidelines

Books

Omer S, Cornwell LD, Bakaeen FG. Acquired heart disease: coronary insufficiency. In: Sabiston textbook of surgery. Amsterdam: Elsevier. p. 1658–90.

Off-Pump Coronary Artery Bypass Grafting

16

Shahzad G. Raja and Umberto Benedetto

High Yield Facts

- Many pioneering myocardial revascularization procedures were performed on the beating heart.
- Off-pump coronary artery bypass grafting was revived two decades ago as a strategy to minimize the deleterious effects of cardiopulmonary bypass.
- Off-pump coronary artery bypass grafting is a highly scrutinized surgical technique.
- Major randomized controlled trials validate the safety and efficacy of off-pump coronary artery bypass grafting.
- Modern randomized controlled trials confirm comparable outcomes for off-pump and on-pump coronary artery bypass grafting.
- Concerns about incomplete revascularization, graft patency, inferior long-term survival and the technically demanding nature of off-pump coronary artery bypass grafting have precluded its universal adoption.
- Off-pump coronary artery bypass grafting has a steep learning curve that can be safely negotiated with appropriate patient selection, individualized grafting strategy, peer-to-peer training of the entire team, and graded clinical experience.

Introduction

Despite large increases in percutaneous coronary intervention volumes and an associated decline in surgical revascularization rates, coronary artery bypass grafting (CABG) remains the standard of care for patients with three-vessel or left main coronary artery disease [1]. Conventional CABG performed on cardiopulmonary bypass (CPB) termed on-pump CABG is regarded as the gold standard [2]. However, on-pump CABG results in several physiologic derangements including but not limited to thrombocytopenia, activation of complement factors, immune suppression, and inflammatory responses leading to organ dysfunction. Furthermore, manipulating an atherosclerotic ascending aorta during cannulation and cross-clamping can predispose to embolization and stroke risk [2]. Recognition of these detrimental effects of on-pump CABG resulted in resurgence of off-pump CABG nearly two decades ago [3].

Off-pump CABG since its resurgence has been a subject of intensive scrutiny and speculation. Despite numerous retrospective nonrandomized studies, prospective randomized trials, and meta-analyses validating the safety and efficacy of off-pump CABG [4], the larger and more modern randomized trials have failed to show an outright superiority of off-pump CABG over on-pump CABG [5–8]. In fact, concerns about incomplete revascularization, graft patency and long-term survival have precluded its universal adoption [8, 9]. This chapter provides an overview of the evolution, technique, and outcomes of off-pump CABG as well as concerns and controversies associated with it.

Evolution

Off-pump CABG is often regarded as a recent advancement; however, the history of coronary surgery reveals that many pioneering revascularization procedures were performed on the beating heart (Table 16.1). Vineberg recommended implantation of the left internal mammary artery (LIMA), Vineberg procedure, directly into the ischemic heart muscle, without circulatory assistance [10]. The first reported coronary revascularization, by Bailey in 1957 [11], and also the one reported a year later by Longmire [12], described techniques of endarterectomy performed on the beating heart. Although Favaloro, in 1968, popularized coronary artery bypass with saphenous vein grafts using pump support [13],

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Kolessov reported using the LIMA for coronary bypass without the pump, in 1967 [14]. In 1975, Trapp and Bisarya [15] and also Ankeney [16] presented their landmark reports of operations, performed without CPB, for disease of the right and left anterior descending coronary arteries. At about the same time, the safety of perfusion techniques was standardized, and methods of myocardial protection by means of cold cardioplegia were developed. As a result, most surgeons abandoned off-pump surgery: there were technical advantages to operating on an arrested heart in a dry field, and there were concerns about the risk of myocardial injury during temporary coronary occlusion in the beating heart [17].

Table 16.1 Evolution of off-pump coronary artery bypass grafting

Year	Development
1876	Adam Hammer establishes the pathophysiology of coronary artery disease
1910	Alexis Carrel first describes coronary artery bypass grafting in animals
1950	Vineberg first to implant internal mammary artery into the myocardium
1953	D.W. Gordon Murray reported experimental placement of arterial grafts into the coronary circulation
1955	Sidney Smith first to harvest long saphenous vein and use it as an aorto-coronary conduit
1957	Bailey reports first successful coronary endarterectomy in man on beating heart
1958	Longmire reports another open coronary endarterectomy without cardiopulmonary bypass
1960	Goetz et al. reported non-suture method using tantalum rings for coronary anastomosis
1964	Kolesov performs successful internal mammary artery to coronary artery anastomosis in humans on the beating heart
1967	Favaloro performs successful coronary artery bypass grafting in humans using saphenous veins
1990s	Benetti, Calafiore, Subramanian achieve direct anastamoses between left internal mammary artery and left anterior descending artery on beating hearts, operating through 10 cm incision between ribs
1995	Launch of products to enable beating heart multivessel coronary artery bypass grafting through median sternotomy
1997	Octopus®, the first tissue suction stabilizer for beating heart coronary artery bypass grafting launched
1998	Duhaylongsod, Mayfield and Wolf report successful thoracoscopic harvesting of left internal mammary artery at various centers
2000	Falk, Diegeler, Walther, Auschbach and Mohr report a succession of developments in minimally invasive robotic surgery

In 1990s, there was a renewed interest in performing off-pump CABG [18]. Recognition of the deleterious effects of CPB accompanied by evolution of techniques and technology to perform off-pump CABG safely led to this resurgence. In the United States, the popularity of off-pump CABG peaked in 2002, when it constituted approximately 23% of CABG procedures and then declined to 17% by 2012 [19]. However, there is wide variability worldwide, and the whole field is subject to large swings based on new technology and new outcome studies.

Technique

A standard median sternotomy is required for off-pump multivessel grafting [20]. Median sternotomy allows access to all potential targets, including routine access to the left or right internal mammary arteries for harvesting, and permits rapid institution of CPB should instability occur during CPB [18].

Cardiac displacement allows the exposure of posterior, lateral, and inferior targets and can be achieved either by the placement of deep pericardial retraction sutures or the use of stockinet sutured into the oblique sinus [21]. Exposure of the left anterior descending (LAD) artery, its diagonal branches, or proximal right coronary artery (RCA) can be achieved with minimal displacement by placing laparotomy sponges in the pericardial sac [22] (Fig. 16.1). To expose the circumflex artery, its branches, the posterior descending artery, and the posterolateral branch of the RCA, a combination of maneuvers and

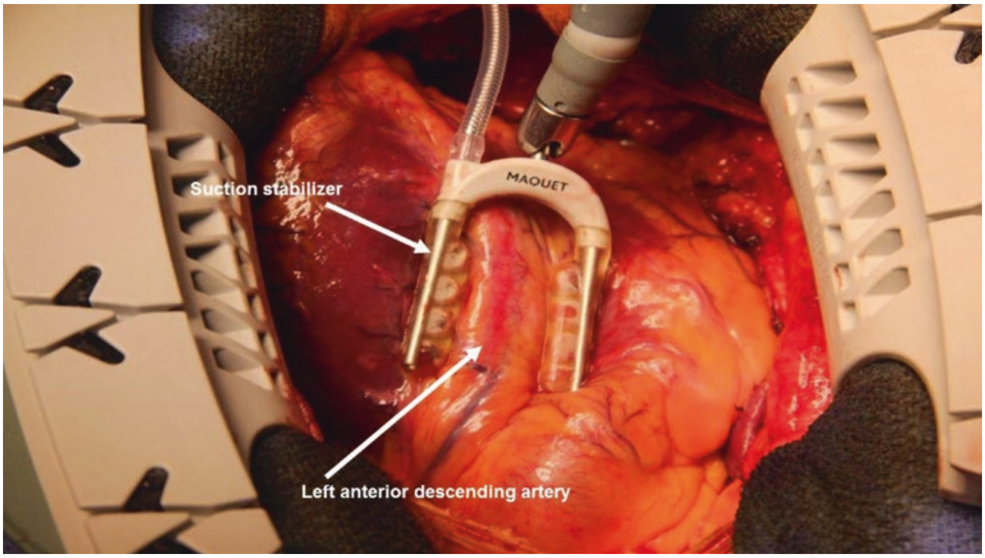

Fig. 16.1 Exposure of the left anterior descending artery

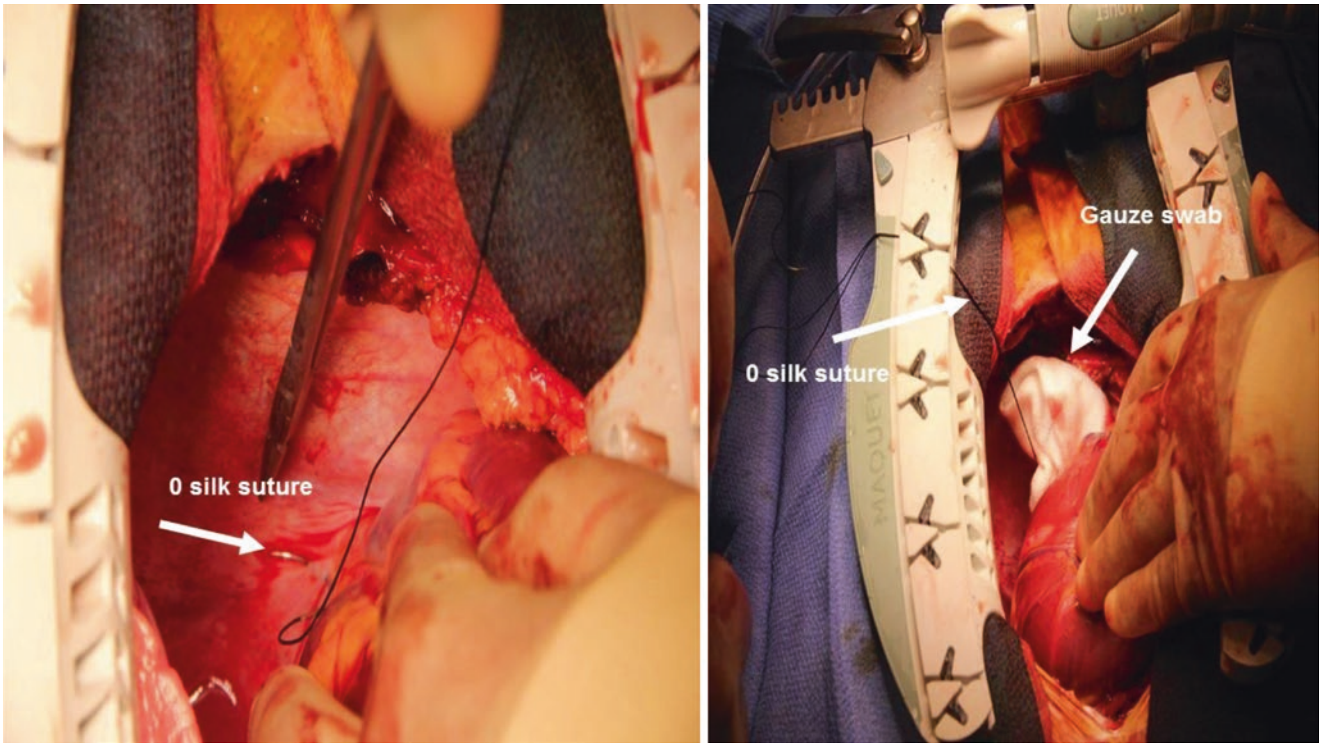

Fig. 16.2 Placement of single 0 silk suture in the pericardium next to inferior vena cava (left) and use of suture with a protective gauze swab for exposure of first obtuse marginal branch

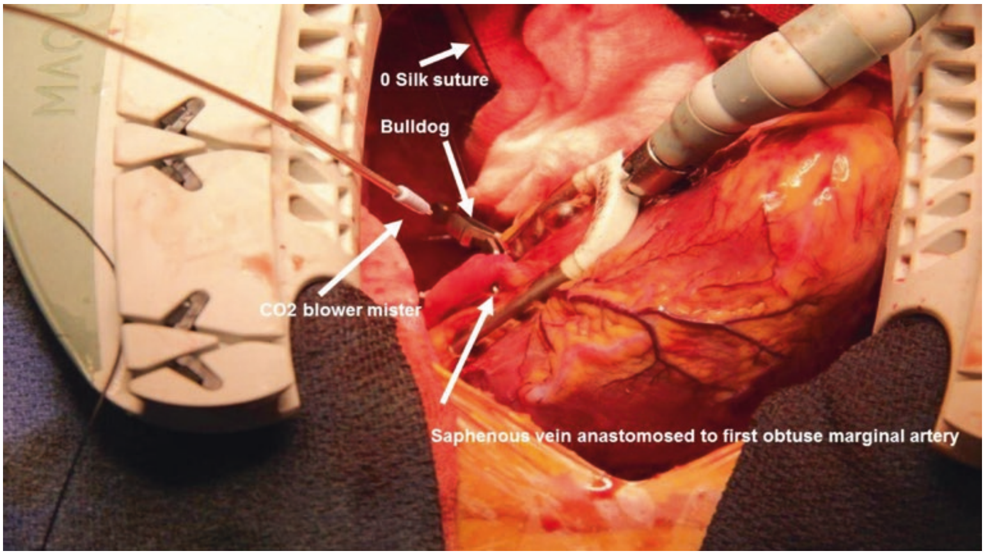

Fig. 16.3 Setup for exposure and grafting of lateral wall target vessel

techniques, including placement of pads, slings, pericardial sutures, or a retracting sock [18] may be used (Fig. 16.2). The heart is displaced and elevated anteriorly as a result of these maneuvers, thereby providing adequate exposure (Fig. 16.3).

The key to successful off-pump grafting is effective local cardiac wall stabilization, which allows good quality anastomotic suturing. Stabilizers placed on the epicardium over the planned site of arteriotomy reduce cardiac motion either by pressure or suction devices [18]. This is a huge advancement from the early days, when bradycardia was induced with short-acting beta-blockers, diltiazem, or adenosine to produce a quiet anastomotic site [18]. Several stabilizers have gained acceptance with graft patency similar to that of conventional CABG [23]. The coronary artery stabilizer is placed on the epicardium, over the planned site of arteriotomy to provide regional immobilization.

A bloodless field is an essential prerequisite for safe coronary anastomosis. A variety of strategies including silastic snares or sutures, clamps, or coronary occluders have been employed to achieve a bloodless field [18] (Fig. 16.4). These techniques also

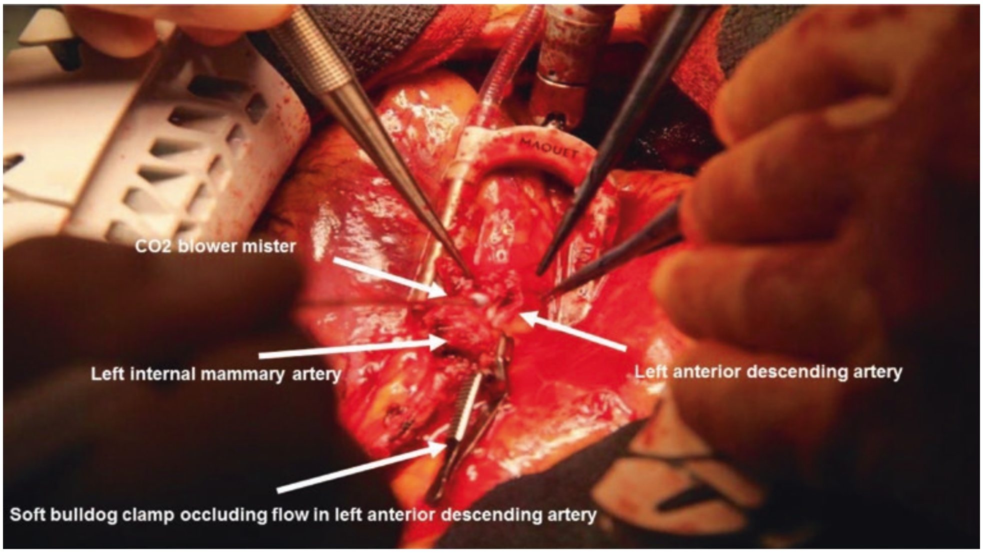
CO2 blower mister
Left internal mammary artery
Left anterior descending artery
Soft bulldog clamp occluding flow in left anterior descending artery
MAQUET

Fig. 16.4 Use of soft vascular bulldog clamp for inflow occlusion in left anterior descending artery and CO_2 blower mister for enhanced visualization

allow preconditioning if required. Intravascular shunts are now more commonly used with the advantages of maintenance of coronary perfusion, prevention of ischemia, reduced back bleeding, and visualization of suture line to prevent accidental suturing of the posterior coronary wall [24]. Visualization is also enhanced by using a surgical blower-humidifier with a gas and fluid administrative set connected to a regulated gas source of carbon dioxide [25].

Anesthetic Considerations

Anesthesia for off-pump surgery is conducted using the same principles that apply to cardiac surgery under CPB, which include safe induction and maintenance of general anesthesia with a technique that offers maximum cardiac protection [18]. Knowledge of the coronary anatomy, surgical plan, and good communication between the surgeon and anesthesiologist is vital [21]. Important considerations include prevention and management of ischemia and hemodynamic instability during occlusion of native coronary arteries, adequate postoperative analgesia, early emergence, extubation, and ambulation. Hypothermia needs to be aggressively prevented [18]. A cell saver may be used to reduce homologous blood transfusion in multivessel off-pump CABG. Transvenous pacing leads, defibrillator paddles, and facilities for intra-aortic balloon counterpulsation or emergency CPB should be available [18]. A variety of strategies are employed to avoid hemodynamic instability and emergency conversion (Table 16.2).

There are divergent opinions regarding the appropriate dose of heparin for off-pump CABG, ranging from full heparinization to more modest doses. It is generally held that an activated coagulation time >300 s is adequate, and this should be fully reversed at the end of surgery with an appropriate dose of protamine [18].

Table 16.2 Strategies to prevent hemodynamic instability

• Extensive right pleurectomy
• Deep vertical right pericardiotomy
• Gentle right decubitus Trendelenburg position
• Ischemic preconditioning
• Constructing the proximal before the distal anastomosis
• Revascularizing the territory of the LAD before lifting or turning the heart
• Avoidance of surgery on the main right coronary artery instead grafting its posterior descending branch
• Pacing wires may be prophylactically sited in the right atrium or ventricle to overcome bradyarrhythmia
• Prophylactic intra-aortic balloon pump placement for high-risk cases

Indications

With rapid improvement in surgical technique and advances in technology, off-pump CABG is being used for an increasing number of patients Indications for off-pump CABG include single as well as multivessel coronary artery disease as well as a hybrid procedure with percutaneous coronary intervention [18] and transcatheter aortic valve replacement [26]. Surgical advances in recent years with improved surgical expertise have resulted in the inclusion of patients with the following comorbidities (Fig. 16.5): low left ventricular ejection fraction, left mainstem disease, advanced age, stroke, chronic renal failure, chronic obstructive pulmonary disease, sleep apnea syndrome, atheromatous disease of the aorta, acute myocardial infarction, and reoperations [18]. Off-pump CABG as a combined procedure has been done with transmyocardial laser revascularization, carotid endarterectomy, abdominal aortic aneurysm repair, lung surgery, gastrectomy [18] and is also reported as a strategy to reduce CPB and aortic cross clamp time for patients requiring concomitant valvular surgery [27].

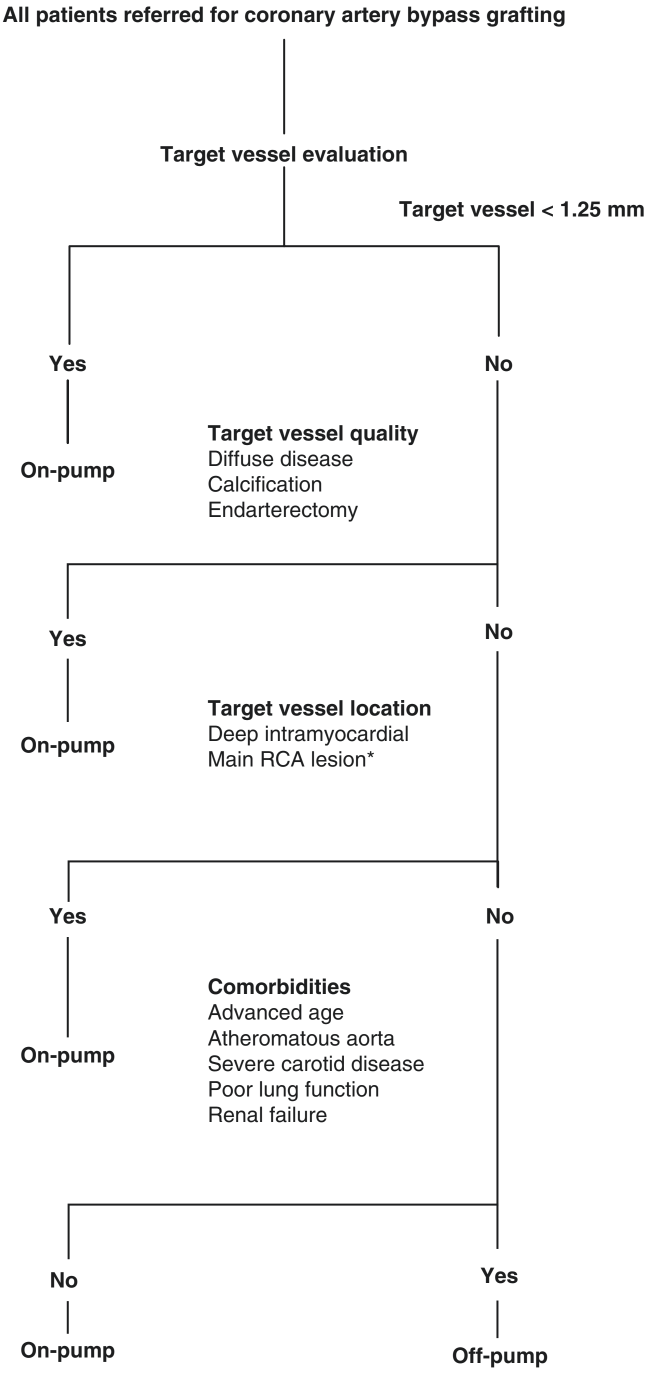
All patients referred for coronary artery bypass grafting
Target vessel evaluation
Target vessel < 1.25 mm
Yes
No
On-pump
Target vessel quality
Diffuse disease
Calcification
Endarterectomy
Yes
No
On-pump
Target vessel location
Deep intramyocardial
Main RCA lesion*
Yes
No
On-pump
Comorbidities
Advanced age
Atheromatous aorta
Severe carotid disease
Poor lung function
Renal failure
No
Yes
On-pump
Off-pump

Fig. 16.5 Decision-making algorithm for choice of surgical strategy (*RCA* right coronary artery). *Poor distal targets necessitating grafting of main body of right coronary artery

Contraindications

In general, the contraindications of off-pump CABG are few and can be divided into absolute and relative (Table 16.3). Despite advances in surgical techniques and technology, exposure of the posterior wall vessels can be potentially difficult, especially in a patient with poor ventricular function or when the surgeon has not traversed the learning curve. Inadequate exposure of the target results in fewer number of distal anastomoses and incomplete revascularization.

Table 16.3 Contraindications of off-pump coronary artery bypass grafting

Absolute contraindications
• Cardiogenic shock
• Major ischemic arrhythmias
Relative contraindications
• Small, deep intramyocardial target vessels
• Calcified target vessels
• Poor ventricular function
• Patients with deep pectus excavatum
• Marked leftward displacement or rotation of the heart
• Reoperation

In a patient in cardiogenic shock with a failing heart, placement on the CPB is unavoidable to prevent further end organ damage, and the role of off-pump CABG is limited because of hemodynamic instability [28]. If the patient is experiencing global ischemia, pump failure and unstable hemodynamics, off-pump CABG should not be performed.

The reasons for incomplete revascularization could be the quality of the target vessel, such as a small, heavily calcified, or intramyocardial coronary artery [29]. Grafting of these small coronary arteries and/or calcified arteries is challenging, even during on-pump CABG with cardiac arrest. Tedious endarterectomy of calcified vessels should be performed on CPB. Extensive dissection of an intramyocardial coronary artery on the beating heart carries risk of ventricular rupture and should be performed with a decompressed heart on CPB. A hybrid procedure involving off-pump CABG and percutaneous intervention could be an option in these difficult patients.

Outcomes

Since its revival, off-pump CABG has been under the microscope of skeptics. It has always been the focus of scientific scrutiny, and current medical literature contains a staggering amount of research related to this technique. In fact, among modalities of myocardial revascularization, off-pump CABG is perhaps the most rigorously tested technique [30]. There is plenty of high-quality evidence from large observational studies [31–35], single institutional randomized controlled trials [36–40] as well meta-analyses and systematic reviews validating the safety and efficacy of off-pump CABG [41–45]. Majority of the published evidence comparing on-pump and off-pump CABG has shown comparable outcomes for these two techniques. However, inability of small, prospective, randomized controlled trials that have lacked sufficient

Table 16.4 Comparison of off-pump CABG with on-pump CABG in recent randomized controlled trials

Trial	30-Day mortality	Stroke	Myocardial infarction	Renal failure	Reoperation for bleeding	Similar index of completeness of revascularization	Repeat re-intervention	1-Year survival	5-Year survival
CORONARY trial [5]	Same	Same	Same	Same	Less	Yes	More	Same	Same
GOPCABE trial [6]	Less	Less	Less	Less	Less	No	NM	NA	NA
DOORS trial [7]	Same	Same	Same	Same	Same	Yes	NA*	NA	NA
ROOBY trial [8]	Same	Same	Same	Same	Same	No	More	Less	Less
On-off study [52]	Less	Less	Less	Less	Less	Yes	NM	NA	NA
The Best Bypass Surgery trial [53]	Same	Same	Same	Same	Same	Yes	Same	NA	Same+

CABG coronary artery bypass grafting, *Less* less with off-pump CABG, *More* more with off-pump CABG, *same* same with off-pump and on-pump CABG, *NA* not available, *NA** more graft occlusion with off-pump CABG, *NM* not measured, + 3-year survival

sample size to demonstrate differences in early and long-term outcomes coupled with misperceptions and misconceptions about incomplete revascularization, reduced long-term graft patency and increased need for repeat revascularization resulting in inferior long-term survival [9] have prompted opponents of off-pump CABG to demand abandonment of this technique [46]. Those who question the feasibility and utility of off-pump CABG completely ignore the fact that larger observational studies [47–51].and recently conducted multi-institutional randomized controlled trials that are better powered to statistically compare outcomes have shown more favorable in-hospital outcomes and equivalent long-term outcomes [5–7, 52, 53] with off-pump and on-pump CABG (Table 16.4).

In the current era increasing number of patients with high-risk profile are being referred for CABG. The benefits of off-pump CABG are apparent for patients at high risk for complications associated with CPB and aortic manipulation. Recent studies have demonstrated improved outcomes in higher-risk patients undergoing off-pump CABG [52–56]. In view of changing patient profile, off-pump CABG remains a valuable option for patients deemed high-risk for conventional CABG.

Concerns

Graft failure is one of the major determinants of clinical prognosis after CABG. There has been considerable concern among surgeons and cardiologists that the greater technical difficulty of off-pump coronary revascularization might translate into less precise anastomoses and subsequently diminished graft patency [57]. With conventional on-pump CABG, the 15-year patency rate is >97%. This is the gold standard that any new revascularization method must compete against [58]. A steep learning curve, distractions caused by cardiac motion or pulmonary insufflations, and construction of anastomoses on a moving target have been implicated as factors responsible for inferior graft patency after off-pump CABG [58].

Interestingly, all concerns about quality of anastomoses and suboptimal graft patency over the years have been predominantly attributed to two randomized controlled trials [8, 59]. Shroyer et al. [8] demonstrated that the patency rate of the off-pump arm was lower than that of the on-pump arm on 12-month angiography, and the 1-year composite adverse outcome rate (death from any cause, nonfatal myocardial infarction, and any reintervention procedure) was higher for off-pump than for on-pump CABG. Such findings do not come as a surprise since the 53 participating surgeons enrolled on average only eight patients per year during the study period and had unacceptably high conversion rates to on-pump surgery (12%) and incomplete revascularization (18%). Moreover, in 60% of the cases a resident was the primary surgeon again raising concerns about the relative inexperience translating into poor graft patency. Another unrecognized confounder that contributed to poor graft patency in the ROOBY trial [8] was the concomitant use of endoscopic vein harvesting (EVH) in 1471 patients (on-pump = 907 and off-pump = 564). The incidence of a patient having one or more occluded saphenous vein grafts on follow-up angiography was 41.3% in the EVH group, compared with 28.0% in the open vein harvesting (OVH) group ($P < 0.0001$). Overall saphenous vein graft patency in the EVH group was 74.5%, which was significantly worse than the 85.2% rate in the OVH group ($P < 0.0001$) [60]. Since ROOBY trial was recruiting at a time when EVH was not being widely practiced the poor vein graft patency secondary to EVH can be attributed to learning curve and relative inexperience of the vein harvesters. Poor conduit quality, a consequence of the learning curve for EVH, has been shown to be a predictor of early graft failure, blunted positive remodeling, and greater negative remodeling [61].

The other frequently cited randomized trial supporting the argument of poor graft patency after off-pump CABG is the trial by Khan et al. [59] reporting decreased patency at 3 months in the off-pump group. However, closer analysis of this reveals that limited experience of the operating surgeons, consisting of only 98 off-pump procedures, which require a different skill set, during the 2 years before the study (an average of 25 procedures per surgeon per year) coupled with the relatively low dose of intraoperative heparin, the absence of aggressive antiplatelet therapy with clopidogrel postoperatively, and the failure to use new suction devices to optimize exposure were perhaps some of the confounding factors for poor graft patency [4, 62].

Controversies

Fewer grafts resulting in incomplete revascularization is a controversy that has plagued off-pump CABG since its revival. The criticism regarding completeness of revascularization is no longer valid in the current era as technology to safely perform multivessel off-pump CABG has improved tremendously over the past decade. Grafting of vessels on the lateral and inferior aspects is no longer impossible. In fact, the majority of evidence from randomized trials suggests at least equivalent completeness of revascularization [5–7, 52, 53]. Furthermore, it is equally important to understand that completeness of revascularization and number of grafts should not be used synonymously. A more logical way to address the issue of completeness of revascularization is to use the index of completeness of revascularization [number of grafts performed divided by the number of grafts needed (number of graftable vessels with angiographically significant stenoses)] [63].

It is important to emphasize that the frequency of complete revascularization reported by various studies comparing off-pump and on-pump CABG is always influenced by relative experience with each technique of the reporting center(s) and surgeon(s). For example, centers where on-pump CABG is used for most cases, and off-pump CABG is used for only a few cases the rates of complete revascularization in the late *vs* early off-pump experience will remain the same highlighting the importance of learning curve as well as case load. Such centers can also have an impact on the final completeness of revascularization achieved by multicentre randomized trials. This fact is exemplified by the Veterans Affairs (VA) Randomized On/Off Bypass (ROOBY) trial [64]. Every year, approximately 4000 isolated CABG procedures are performed in the VA system at 42 cardiac surgery facilities [65]. During the recruitment period of the ROOBY trial only 7 of the 42 centers qualified as high-volume off-pump CABG centers performing at least 50 off-pump cases per year [66]. Since the recognized learning curve for off-pump CABG is between 50 and 75 cases [67] it is not surprising that the ROOBY trial reports incomplete revascularization with off-pump CABG.

Off-pump CABG is suggested to be associated with an increase in long-term all-cause mortality. The negative impact of incomplete revascularization and lower graft patency on late mortality rates is well-recognized [68]. Takagi et al. [69] recently published a meta-analysis of 11 randomized trials demonstrating a statistically significant increase in ≥1 year all-cause mortality by a factor of 1.37 with off-pump relative to on-pump CABG (RR = 1.373; 95%CI: 1.043–1.808). It is extremely important to highlight that the sensitivity analysis in this meta-analysis revealed that the ROOBY trial [8] strongly contributed to the pooled estimate. The aforementioned criticisms of this trial provide an explanation for the inferior survival of off-pump cohort. Furthermore, majority of the recently conducted trials reporting 30-day mortality [5–7, 52, 53] have not yet reported outcomes for long-term follow-up.

It is expected that once longer follow-up data is available for recently conducted randomized trials [5–7, 52, 53], that utilized newer technology for stabilization and exposure and had similar index of completeness of revascularization for off-pump and on-pump CABG, these controversies will be resolved.

Conclusion

Despite numerous clinical studies validating the benefits of off-pump CABG, skepticism persists regarding the safety, efficacy, and equivalence of revascularization with off-pump CABG compared with on-pump CABG. Off-pump CABG is a technically demanding strategy and central to all the concerns and controversies associated with this technique is the issue of learning curve. The learning curve of off-pump CABG can be safely negotiated with appropriate patient selection, individualized grafting strategy, peer-to-peer training of the entire team, and graded clinical experience (preoperative planning, adequate exposure, proximal anastomoses to the aorta, and distal anastomoses initially to anterior wall vessels, followed by inferior wall vessels and then lateral wall vessels). Both on-pump and off-pump CABG have their place in the field of myocardial revascularization. Changing profile of patients that are being referred for surgical revascularization necessitates that present day cardiac surgeons are appropriately trained to perform off-pump CABG.

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Minimally Invasive Coronary Artery Bypass Grafting

17

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High Yield Facts

- Minimally invasive coronary artery bypass grafting (CABG) is developed to allow adequate exposure and complete revascularization through a small thoracotomy incision without cardiopulmonary bypass.
- The success of a minimally invasive CABG procedure also requires cooperation between the surgeon, anesthesiologist, and perfusionist and diligent management of hemodynamics.
- Multiple prospective and retrospective observational studies have been published on the experience with minimally invasive CABG, with both short and long-term results.
- Minimally invasive CABG is a safe alternative to full sternotomy CABG with comparable early and long-term postoperative mortality and morbidity.
- Minimally invasive CABG has significantly shorter length of hospital stay and earlier postoperative physical recovery compared to full sternotomy CABG.

Introduction

The invasiveness of coronary artery bypass grafting (CABG) has remained largely unchanged since its initial introduction. Although full sternotomy is still considered as the gold standard incision for various cardiac conditions, there is considerable morbidity related to its use and to that of cardiopulmonary bypass (CPB), including infection, stroke, re-operation, transfusion, acute kidney injury, and a slow return to full physical activity [1, 2]. In coronary surgery, the development of minimally invasive technique has been limited by difficulty in accessing and performing anastomosis on multiple different areas of the heart through a single small incision, especially on a beating heart or in obese patients [3]. Minimally invasive CABG has been developed to allow adequate exposure for surgical precision, and complete revascularization via a small thoracotomy incision without CPB. This chapter will review the literature that has been published over the past decade about minimally invasive CABG and the technical aspects of the procedure.

Published Literature

Minimally invasive CABG was developed to avoid the drawbacks of sternotomy, while allowing for complete revascularization for multi-vessel coronary disease without the need for costly equipment. In 2009, McGinn and Ruel reported on the safety and feasibility of Minimally invasive CABG in a prospective study of their dual-centre experience in 450 patients [4]. Complete revascularization was achieved in 95% of patients, with a mean of 2.1 ± 0.7 grafts. The rate of perioperative mortality was 1.3%, 3.8% required conversion to sternotomy, 7.6% required the use of CPB, and the mean hospital stay length was 5.9 ± 3.4 days. At a mean follow up of 19.2 ± 9.4 months, 3% of patients required revascularization by percutaneous coronary intervention (PCI). This study was the first large report where a minimally invasive multi-vessel CABG approach compared favorably with the results of a standard CABG operation.

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The angiographic patency of grafts after minimally invasive CABG was systematically evaluated in 91 patients from two centres [5]. The median number of grafts was 3, and complete revascularization was achieved in all patients. No peri-operative mortality was observed. The median length of hospital stay was 4 days, and at 6 months follow up, there were no mortality or major adverse cardiac events (MACE). Computer tomogram (CT) angiography was used at 6 months follow up to assess graft patency, and the overall graft patency was 92%, with 100% for left internal thoracic artery (LITA) grafts and 85% for saphenous vein grafts. Furthermore, in 2013, Nambiar and Mittal described their experiences with 150 patients who underwent minimally invasive CABG with bilateral internal thoracic arteries (BITA) composite Y grafts [6]. The graft patency at 90 days follow up was 100% in those patients who underwent either conventional coronary angiogram or CT angiogram.

As a result of its technical complexity, the learning curve and its association to patient outcome were examined [7]. Single-vessel and multivessel revascularization with or without CPB assist was performed in 210 consecutive minimally invasive CABG cases, and the outcomes between the first 25 cases and the remainder cases were compared. It was found that experience or lack thereof was not associated with 1-month clinical outcomes (mortality, myocardial infarction, reopening for bleeding or graft revision, revascularization) in any of the techniques. Therefore, it was concluded that surgeons with enough experience of off-pump coronary artery bypass (OPCAB) grafting can initiate minimally invasive CABG safely, and that CPB assistance is a good option to avoid conversion to sternotomy and alleviate a significant learning curve when initiating a multivessel minimally invasive CABG program.

The potential benefits of minimally invasive CABG via a small left thoracotomy over conventional OPCAB via sternotomy were examined in multiple studies. In two case-matched studies, there were no significant differences in early mortality and post-operative morbidity such as atrial fibrillation, acute renal failure, and cerebrovascular accidents [8, 9]. In addition, minimally invasive CABG was found to have statistically significant lower peri-operative transfusion rate and shorter length of stay compare to OPCAB. Lapierre et al. found that patients who underwent minimally invasive CABG had significantly fewer wound infections and a shorter time required to return to full physical activity (12 days vs. 36 days), while Rabindranauth et al. showed no significant difference in long-term survival between minimally invasive CABG and OPCAB with a mean follow up of 18.5 ± 11.5 months and 45.0 ± 27.8 months for minimally invasive CABG and OPCAB, respectively. Furthermore, Ziankou and Ostrovsky compared the long-term outcomes of minimally invasive CABG to OPCAB as well to standard on-pump CABG via sternotomy in a propensity score-matched study [9]. The minimally invasive CABG group had significant less intra-operative blood loss compare to OPCAB and standard CABG, and a lesser incidence of blood transfusion than the OPCAB group. The minimally invasive CABG group also had less wound infection than OPCAB (4% vs. 9.9%, respectively), and a shorter length of stay compare to standard CABG (4.5 days vs. 7.5 days, respectively). The median time to return to full physically activity was also significantly shorter in the minimally invasive CABG group compare to the OPCAB and CABG groups (14 days vs. 56 days vs. 56 days, respectively). Finally, at a mean follow up of 40.3 ± 15.6 months for minimally invasive CABG, 48.8 ± 21.3 months for OPCAB, and 63.9 ± 25.9 months for standard CABG, there were no significant differences in mid-term survival and cumulative major adverse cardiac and cerebrovascular events (MACCE) between minimally invasive CABG and OPCAB, and between minimally invasive CABG and standard CABG.

The effectiveness of minimally invasive CABG in patients greater than 75 years old was also compared to full sternotomy CABG and PCI [10, 11]. Among the 159 patients who received either minimally invasive CABG or full sternotomy CABG over 3 years, minimally invasive CABG had a significantly lower 5 year all-cause mortality than full sternotomy CABG, and Kaplan–Meier curves also showed significantly higher overall survival in the minimally invasive CABG group compared with full sternotomy CABG. On the other hand, among 175 elderly patients who received either minimally invasive CABG or PCI at the same centre, no significant difference in long-term all-cause mortality were observed between the two groups, and Kaplan-Meier curves showed similar 5-year survival. However, the rate of repeat revascularization was significantly higher in the PCI group than the minimally invasive CABG group.

Redo-minimally invasive CABG is currently considered as a relative contraindication for the procedure. There is currently no literature, including either retrospective studies or case reports, on this topic. The major concern is the elevated risk of injuring the heart as well as difficult exposure due to adhesions, leading to a much higher hypothetical rate of conversion to sternotomy. As techniques becomes more developed and perfected, redo-minimally invasive CABG could become a future consideration and progression of the procedure.

A number of limitations exist in the aforementioned literature on minimally invasive CABG. Firstly, most of the articles are retrospective observational studies with a small sample size, typically involving a single surgeon from a single centre. Secondly, bias exists in patient selection, especially during the initial experience with minimally invasive CABG, given the number of absolute and relative contraindications proposed in the early phase of the procedure [4]. Even though some authors attempted to address this issue by propensity-score matching or case-matching based on risk profiles, residual bias could still exist. In a few studies, the number of grafts in minimally invasive CABG patients are lower than in other groups, which could be due to the applicability of the procedure in single or double-vessel disease, and could explain some differences in rate of transfusion, wound infection, and post-operative recovery between minimally invasive CABG and other procedures of interest. Thirdly, further long-term follow-up data over the next decade is required, and comparative long-term results concerning the survival rates, quality of life, frequency of major cardiovascular events, and bypass patency need further research. Furthermore, long-term patency of grafts is not addressed. The only graft patency study used CT angiography as the assessment tool at 6 months, without correlation with coronary angiography, which provides better assessment of the distal anastomosis in small sized vessels. Lastly, minimally invasive CABG remains to be a new technique that needs further external validation to establish the generalizability of the procedure. A summary of studies on MICS CABG is included in Table 17.1.

Table 17.1 Summary of literature on minimally invasive CABG

Author (year)	Study type	No.	Results
Lapierre et al. [12]	Retrospective	9	0% in-hospital mortality Median number of grafts = 3 Median length of hospital stay = 4 days Return to full physical activity in 1 month
McGinn et al. [4]	Prospective	450	1.3% in-hospital mortality Mean number of grafts = 2.1 94.9% complete revascularization Mean length of hospital stay was 6 days Target vessel revascularization in 19 months = 3%
Lapierre et al. [13]	Retrospective (MICABG vs. OPCAB)	300	No difference in mortality (0% in-hospital mortality) Median number of grafts = 2 in both groups MICABG had: – Lower transfusion rates – Shorter length of hospital stay – Shorter return to full physical activity (12 days)
Une et al. [7]	Retrospective (first 25 cases vs. later cases)	200	No difference in mortality (0% in-hospital mortality) No significant difference in early clinical events
Nambiar et al. [6]	Retrospective	150	0.6% in-hospital mortality Mean number of grafts = 2.8 Mean length of hospital stay = 3.1 days At 90 days: – 100% patency in 25% of patients who had coronary angiogram – 100% patency in 22% of patients who had CT angiogram – Normal stress test in 53% of patients who underwent stress test
Lemma et al. [14]	Retrospective	137	0% in-hospital mortality; 1.4% mortality at 26 months Mean number of grafts = 2.4 98.6% complete revascularization
Ruel et al. [5]	Prospective	89	0% in-hospital mortality Mean number of grafts = 2.3 100% complete revascularization 92% patency at 6 months with CTA
Rabindranauth et al. [8]	Retrospective (MICABG vs. OPCAB)	280	0% in-hospital mortality in MICABG group MICABG had: – Lower peri-operative transfusion rate – Shorter length of hospital stay – Earlier extubation No significant difference in survival between MICABG and OPCAB at mean follow up of 18.5 months
Ziankou et al. [9]	Retrospective (MICABG vs. OPCAB vs. CABG)	303	0.7% in-hospital mortality in the MICABG group Mean number of grafts = 2.9 MICABG had: – Less intra-operative blood loss – Shorter time to return to full activity (14 days) No significant difference in survival and MACCE at mean follow up of 40.3 months
Barsoum et al. [10]	Retrospective (MICABG vs. CABG for >75 years old)	159	Mean number of grafts = 2.26 Significant higher overall survival (19.7% vs. 47.6%) at mean follow up of 3.7 years
Barsoum et al. [11]	Retrospective (MICABG vs. PCI for >75 years old)	175	No significant difference in survival (21% vs. 31%) at median follow up of 4.9 years MICABG had significantly less requirement for revascularization (3% vs. 15%)

CABG coronary artery bypass grafting, *CTA* computed tomographic angiography, *MACCE* major adverse cardiac and cerebrovascular event, *MICABG* minimally invasive coronary artery bypass grafting, *OPCAB* off-pump coronary artery bypass, *PCI* percutaneous coronary intervention

Technique

The success of minimally invasive CABG in the early phase of development requires the combination of multiple elements; chest anatomy that would provide good exposure of the heart, relatively non-atherosclerotic femoral arteries that allow peripheral cannulation should CPB be needed, ability of the heart to tolerate hemodynamic changes with manual manipulation, the patient's tolerance to single lung ventilation and changes in positive pressure ventilation, adequate target vessel size and quality, and adequate time to allow for a perfect anastomosis. Contraindications are listed in Table 17.2 [4].

History and physical examination are critically important as these help the surgeon to identify patients with significant vasculopathies that may require further imaging, such as CT angiography, to ensure that femoral cannulation would be safe and feasible. It is important to identify these factors when the patient is first evaluated in clinic.

Prior to the start of the surgery, intubation is performed with a double-lumen endotracheal tube or bronchial blocker to allow for single right lung ventilation. It is advisable that a central line be placed on the left side to avoid the risk of right-sided pneumothorax or hemothorax that could affect single lung ventilation. Trans-esophageal echocardiogram (TEE) is important to monitor cardiac function during positioning of the heart. The patient is positioned at 30° right lateral decubitus position, with the left arm elevated over the head using an arm support (Fig. 17.1). The left groin and the right leg should be accessible for femoral cannulation and saphenous vein harvest, respectively. A 4–6 cm curvilinear incision is made starting at the mid-clavicular line of the fourth or fifth intercostal space and extended laterally (Fig. 17.2). Upon entering the pleural cavity, a Thoratrak (Medtronic, Inc., Minneapolis, MN) retractor is inserted to expose the pericardium for division (Fig. 17.3). The cardiac apex is then mobilized for evaluation of coronary targets. It is desirable that the apex be located one intercostal space beneath the incision to allow optimal manipulation of the heart and access to aorta for proximal anastomoses.

The LITA can be taken down with long instruments from a lateral approach under direct vision. A Rultract Skyhook (Rultract, Cleveland, OH) retractor with #1 and #5 blade is used to pull the rib spreader cephalad and left to provide bet-

Table 17.2 Absolute and relative contraindications for minimally invasive CABG

Absolute contraindications
Emergency surgery with hemodynamic compromise
Severe pectus excavatum
Severe pulmonary disease
Relative contraindications
Previous cardiac surgery
Morbid obesity
Severe LV dysfunction
No adequate PDA or marginal branch targets if bypass to these areas is considered
Absence of femoral pulses bilaterally

CABG coronary artery bypass grafting, *LV* left ventricle, *PDA* posterior descending artery

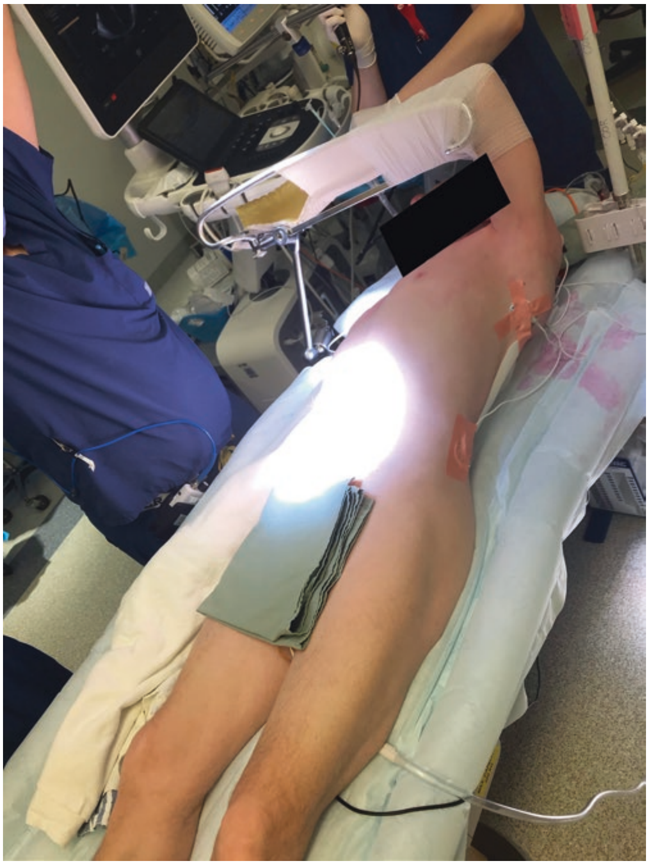
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Fig. 17.1 Patient positioned at 30° right lateral decubitus

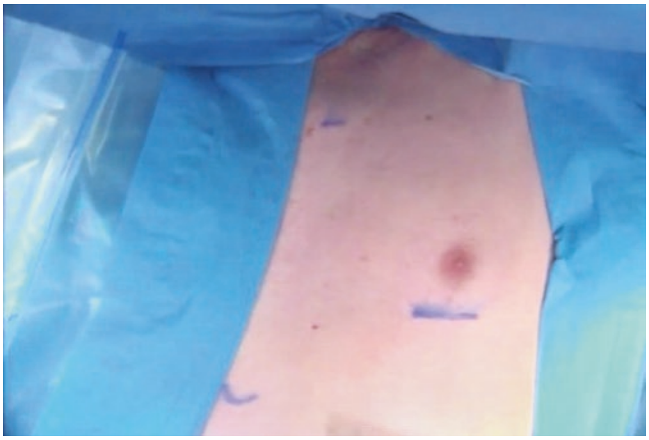

Fig. 17.2 Location of incision for thoracotomy

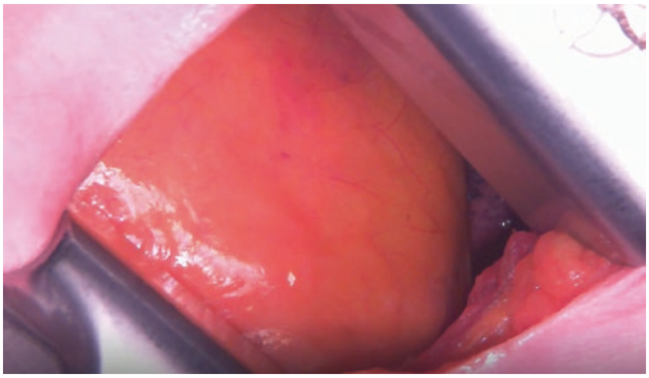

Fig. 17.3 Visualization of heart through the thoracotomy

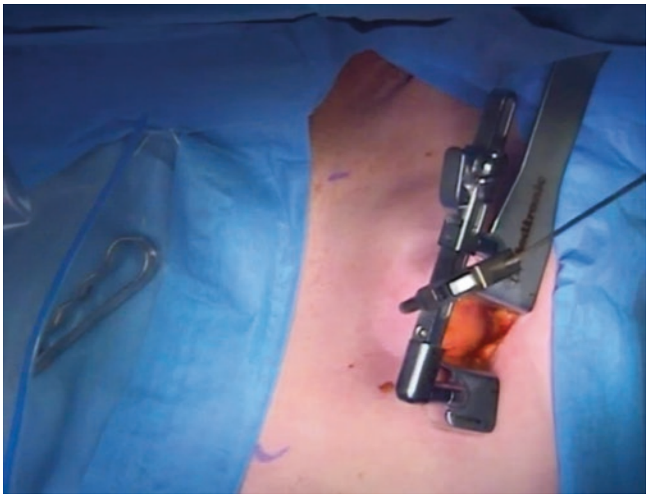

Fig. 17.4 Rultract retractor set up for LITA harvest

ter visualization for proximal LITA dissection (Fig. 17.4). LITA take down usually starts at the mid-portion towards the proximal end; once the LITA is dissected to the subclavian vein, the Rultract skyhook retractor can be re-positioned to pull inferolaterally on the rib spreader to facilitate the dissection of the distal LITA. Heparin is given intravenously before the division of the LITA. The right internal thoracic artery (RITA) is more difficult to access and harvest under direct vision with the small thoracotomy but is now possible as well [6, 15, 16].

Exposure of the aorta for proximal anastomoses can be achieved by a stepwise approach [4, 17]. Firstly, maintaining a central venous pressure between 8 and 12 mmHg to minimize right ventricle filling will improve exposure to the ascending aorta. Meanwhile, increasing the positive end-expiratory pressure (PEEP) on the isolated right lung up to 10–12 cm H_2O hyperinflates the right lung and helps push the aorta towards the mini-thoracotomy. The pericardium is opened towards the aorta and the superior pericardium is retracted inferolaterally towards the mini-thoracotomy with multiple retraction sutures [18]. Pericardial fat anterior to the aorta is removed. An unfolded 4 × 4 gauze can be packed anterior to the superior vena cava against the right lateral aspect of the aorta to further displace the ascending aorta towards the left; alternatively, the posterior ascending aorta can be dissected from the pulmonary artery, and an open 4 × 4 gauze or a half-inch Penrose drain can be passed posterior to the aorta for left anterior retraction [8]. Lastly, a 6–8 mm incision is made in the left sixth or seventh intercostal space in the anterior axillary line to allow introduction of the Octopus Non-Sternotomy Tissue Stabilizer (Medtronic), which is positioned over the right ventricular outflow tract to flatten and displace it towards the left posteroinferior direction; TEE is critically important to ensure there is no right ventricular outflow tract obstruction. The ascending aorta should be visible to the surgeon and a standard partial occlusion clamp can be placed for proximal anastomoses (Fig. 17.5). The evaluation of ascending aorta is performed by CT scan and/or palpation prior to clamping. If significant ascending aortic plaque is palpable, then partial occlusion clamping should be avoided. Alternatively, Y- or T-composite anastomosis between LITA or RITA and other grafts, as well as sequential grafting can be performed to avoid the manipulation of the aorta. The proximal anastomoses can otherwise be performed with running 6-0 polypropylene under direct vision.

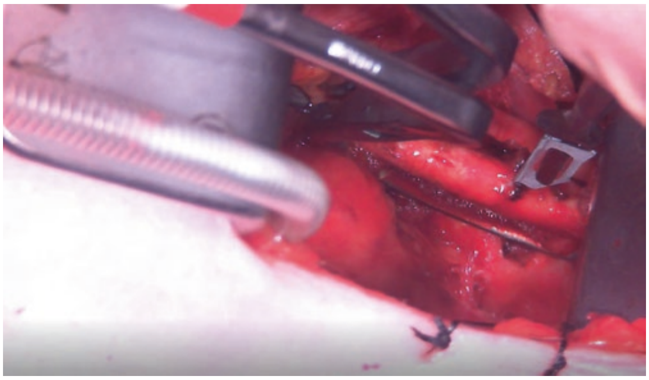

Fig. 17.5 Aortic exposure for proximal anastomosis through the thoracotomy

A Starfish Non-Sternotomy Heart Positioner (Medtronic, Minneapolis, MN, USA) is inserted below the xiphoid process through a 1 cm incision; an “armless” Starfish with its suction cup tied to a Teflon string can also be used to avoid the subxiphoid incision [16] (Fig. 17.6). The left anterior descending artery territory is typically directly visualized underneath the initial mini-thoracotomy with minimal movement of the heart (Fig. 17.7). Retraction of the cardiac apex toward the patient’s left shoulder allows visualization of the posterior interventricular branch of the right coronary artery, while retraction of the apex inferiorly towards the right hip allows visualization of the marginal branches of the cir-

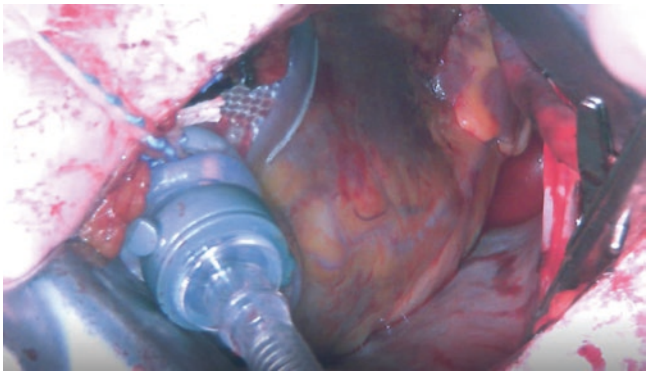

Fig. 17.6 Use of starfish for positioning of the heart

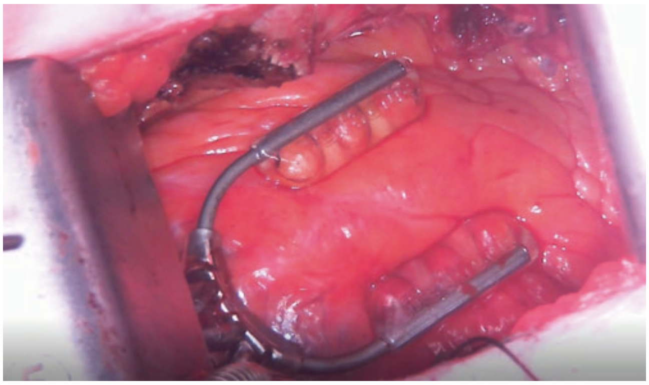

Fig. 17.7 Visualization of the left anterior descending artery through the thoracotomy

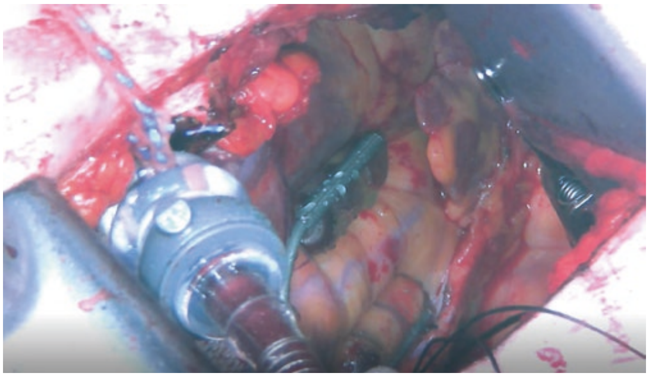

Fig. 17.8 Visualization of the lateral wall through the thoracotomy

cumflex coronary artery (Fig. 17.8). The Octopus epicardial stabilizer helps maintain the target arteriotomy for revascularization in a stable position on a beating heart. If mobilization of the heart position leads to hemodynamic instability despite the use of vasopressors or if the exposure to a distal target is poor, the exposed and prepped left femoral artery and vein is used for peripheral cannulation via a cutdown to initiate CPB [7].

For the distal anastomosis, with epicardial stabilization, a temporary Silastic occluder is placed around the coronary artery to be grafted, proximal to the planned arteriotomy, to control bleeding. A blower mister is used for visualization, and an intracoronary shunt can be inserted into the arteriotomy to promote a relatively dry surgical field and improve precision. The distal anastomoses are performed with 7-0 or 8-0 polypropylene with standard instruments. The flow in each conduit is then assessed with a flow probe. Two Blake drains are placed in all patients in the posterior pericardial space via the subxiphoid incision, and the left pleural space via the seventh intercostal incision. The left lung is re-inflated, and all grafts are inspected under direction vision for malposition or kinking. The thoracotomy incision is closed in the usual fashion.

Conclusion

Minimally invasive CABG is the only non-robotic surgical procedure for coronary artery disease that could combine minimally invasive small thoracotomy with complete arterial revascularization without CPB, which reduces surgical invasiveness, decreases neurological complications associated with aortic manipulation, and avoids the systematic inflammatory response and adverse effects of extracorporeal circulation, without compromising graft patency. Despite the limitations of the current literature, evidence is emerging that minimally invasive CABG maintains equivocal safety profile to traditional full sternotomy CABG as well as OPCAB, while providing superior morbidity profile, such as decrease in peri-operative blood loss and transfusion requirement, rates of wound infection, length of hospital stay and time to return to full physical activity. Furthermore, minimally invasive CABG may help alleviate the patient's fear of cardiac surgery and provides much better cosmesis. Currently, patient selection is an important confounding factor. However, the minimally invasive CABG technique is still within its early phase, and as the technique becomes more widely adopted and surgeons become more experienced, the selection criteria will become more liberalized. The next step involves widening the applicability and utilization of the procedure as well as its evaluation in large multicentre randomized control trials. At the same time, exploration of combination of minimally invasive CABG and robotic techniques, or with PCI in the form of hybrid revascularization could further widen the availability, safety, and complete revascularization in routine multi-vessel coronary surgery [3].

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Totally Endoscopic Coronary Artery Bypass Grafting

18

Brody Wehman and Eric J. Lehr

High Yield Facts

- Robotic totally endoscopic coronary artery bypass grafting (TECAB) has been developed as a sternal-sparing minimally invasive form of coronary revascularization.
- TECAB demands a high degree of coordination and communication amongst the members of a dedicated team.
- There is a significant learning curve for TECAB. The procedure should be introduced and learned in a deliberate and stepwise fashion.
- TECAB can be part of a hybrid revascularization concept to treat multivessel coronary artery disease.
- Procedural and mid-term results seem favorable when compared to standard coronary artery bypass grafting.
- Long-term outcome studies are still needed.

Introduction

Coronary artery bypass grafting (CABG) is an effective method of restoring myocardial perfusion in the setting of complex coronary artery disease. Grafting the left internal mammary artery (LIMA) to the left anterior descending coronary artery (LAD) has been proven to improve long-term survival and multi-arterial grafting may confer additional survival benefits. Traditional CABG requires violation of the sternum to access the cardiac structures and internal mammary arteries (IMAs). Robotic technology provides visualization throughout the entire thorax and facilitates complete total arterial revascularization while maintaining the intact sternum. Robotic assisted totally endoscopic coronary artery bypass (TECAB) has become a reality and a number of highly dedicated centers have adopted the technique. The procedure continues to evolve; indeed, even quadruple vessel CABG has become feasible [1], although multivessel disease is often managed as a hybrid revascularization concept with treatment guided by a heart team. TECAB can be performed on the arrested and beating heart. This approach can be extended to approximately one-third of CABG patients when coronary anatomy is carefully assessed. The purpose of the is chapter is to provide an overview of TECAB, including technical and anesthetic considerations as well as a summary of the learning curve and published outcomes.

Arrested Heart TECAB

TECAB was first performed using cardiopulmonary bypass and cardioplegic arrest. With the heart arrested, anastomoses are constructed on a still heart, eliminating the challenges of working on a moving target. Working space is increased with the heart empty and the lungs deflated [2]. Technical challenges, including bleeding, intramyocardial vessels, myocardial perforation, myocardial ischemia and hemodynamic instability, are easier to manage with cardiopulmonary bypass support. As with all surgical interventions, careful patient selection is important to achieve successful outcomes. Considerations for preoperative work up and patient selection are outlined in Table 18.1.

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Table 18.1 Important overall aspects of preoperative evaluation for totally endoscopic coronary artery bypass (TECAB) surgery

Areas of assessment	Examples of conditions to be ruled out/evaluated	Examples of tests
1. Surgical anatomic suitability	1. Extensive pleural adhesions 2. Previous cardiac or thoracic surgery 3. Narrow intercostal spaces 4. Excessive cardiomegaly	Chest X-ray, chest CT
2. Target surgical lesions' suitability for TECAB		Standard coronary angiography, multidetector row CT
3. Valvular heart disease	Moderate-to-severe aortic insufficiency; severe valvular stenosis or insufficiency, requiring an open combined procedure	Echocardiography
4. Peripheral vascular disease	1. Aortic occlusive disease 2. Tortuous descending aorta 3. Diameter of the femoral vessels 4. Ascending aortic dilation (438 mm) and dissection 5. Atherosclerotic plaque at risk for dislodgement 6. Congenital aortic arch anomalies 7. Carotid/subclavian stenosis	Assessment of peripheral pulses CT angiography of chest, abdomen, and pelvis Echocardiography Doppler ultrasound
5. Ability to tolerate one-lung ventilation	Severe COPD, severe pulmonary hypertension	Functional capacity Pulmonary function tests Chest X-ray Arterial blood gas (on room air)

COPD chronic obstructive pulmonary disease, *CT* computed tomography, *METS* metabolic equivalents, *TECAB* totally endoscopic coronary artery bypass grafting. (Modified from Deshpande et al. [3])

Anesthetic Considerations

Patients are positioned supine with the left hemi-thorax elevated 30°. Sterile defibrillator pads should be positioned to avoid the surgical sites and to allow for sternotomy in the event that conversion is required. One pad is placed over the right pectoralis area and another posteriorly on the left. A double lumen endotracheal tube will achieve single lung ventilation. Alternatively, a bronchial blocker can also be used. Standard invasive monitoring devices are utilized including arterial lines, central lines and transesophageal echocardiography. In some cases, myocardial protection can be augmented with a percutaneous retrograde coronary sinus cardioplegia catheter, although it is not always required. The typical anesthetic setup is demonstrated in Fig. 18.1a. Effective communication between the surgeon and anesthesiologist is critical. A pressurized capnothorax, necessary for optimal surgical exposure may negatively impact the hemodynamic status requiring interventions including fluid resuscitation, vasopressors and inotropes or simply a reduction in the insufflation pressure [4]. These efforts should be coordinated among the entire surgical team. Procedural steps and anesthetic implications are demonstrated in Fig. 18.2.

Fig. 18.1 (**a**) Anesthesia setup demonstrating double lumen endotracheal tube for lung isolation and the transesophageal echocardiography probe. Distal in the right internal jugular vein is the pulmonary artery vent and more proximally the central venous catheter with the retrograde coronary sinus cardioplegia catheter. (**b**) External landmarks guide port placement. The camera port is placed at the midpoint of the sternum and where the ribs fall off the anterior thorax, often in the anterior axillary line. Additional ports are positioned as described. (**c**) The endothoracic fascia is opened and dissected from the internal mammary artery (IMA). If two IMAs are harvested, the right is harvested first to avoid injury to the left. (**d**) Electrocautery at low power is used at a distance from the vessel to divide most side branches of the IMA. The burn can be seen well away from the main vessel. Clips can be used as necessary for large branches. (**e**) After heparinization, the IMA is divided with Potts scissors between clips. (**f**) Transesophageal echocardiography is used to visualize placement and inflation of the endoaortic occlusion balloon. Flow into the coronary ostia can often be seen. (**g**) As the heart is being arrested, and after resection of the pericardial fat pat, the pericardium is opened. The subxiphoid port can be seen at the top of the screen. (**h**) It is critical to properly identify target vessels. The left anterior descending (LAD) artery usually courses horizontally across the screen and slightly higher to the left. When the heart is empty and arrested, the right ventricle sinks down and the LAD can be seen overlying the ventricular septum. Diagonal vessels tend to course towards the lower left corner of the screen. (**i**, **j**) An arteriotomy is made with the robotic lancet blade and extended with Potts scissors. (**k**) The anastomosis begins at the toe, suturing inside out on the graft and outside in on the target, working in a clockwise direction. (**l**) After completing the back wall, both ends of the suture are lifted to tension the suture line. (**m**) Suturing continues around the heel. (**n**) Suture ends are exchanged and the toe is completed suturing outside in on the graft and inside out on the target, counterclockwise towards the heel. (**o**) Transit time Doppler can be used to assess graft flow. (**p**) All surgical sites are carefully inspected and after undocking the robot, port sites can be packed with an absorbable hemostatic agent

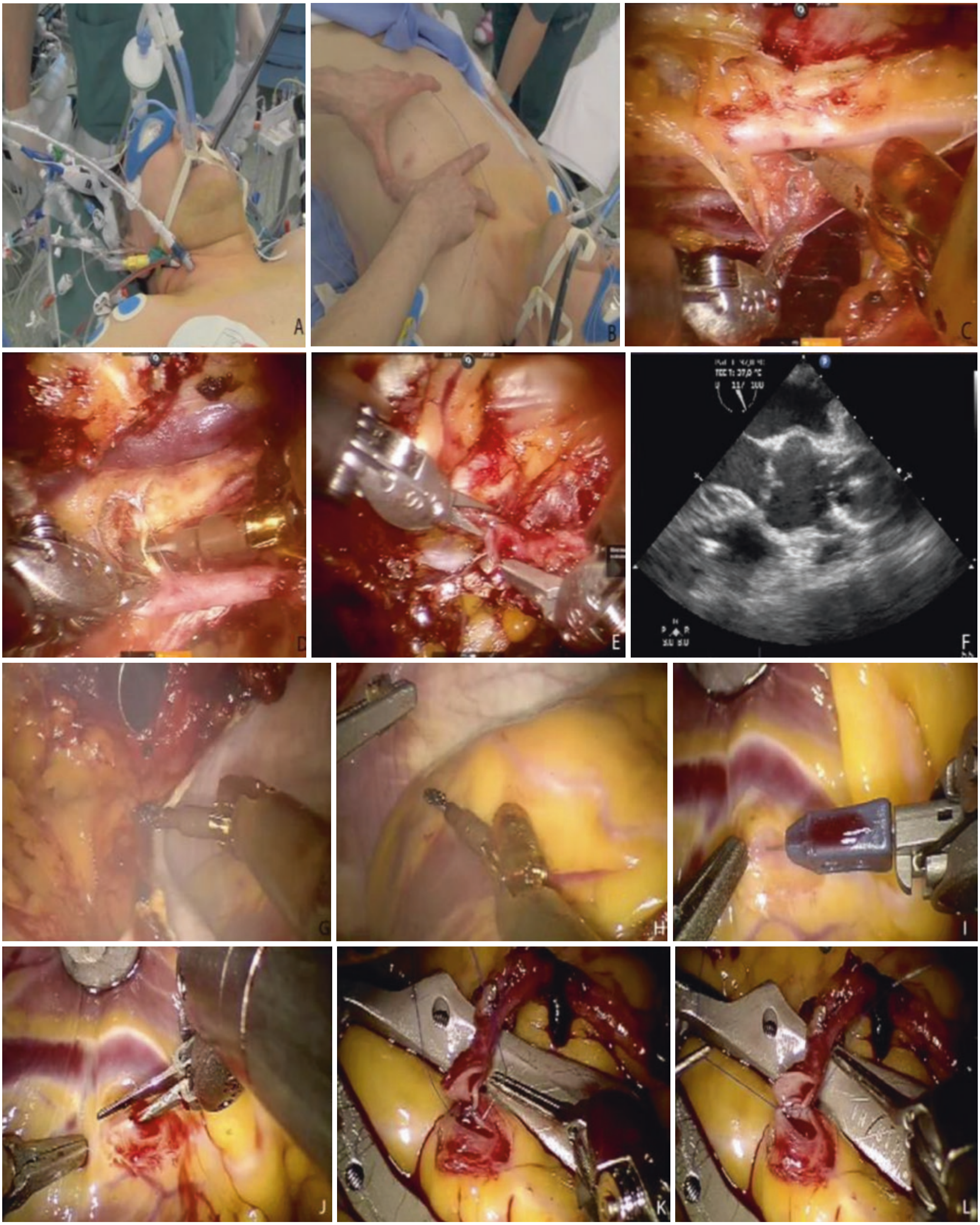
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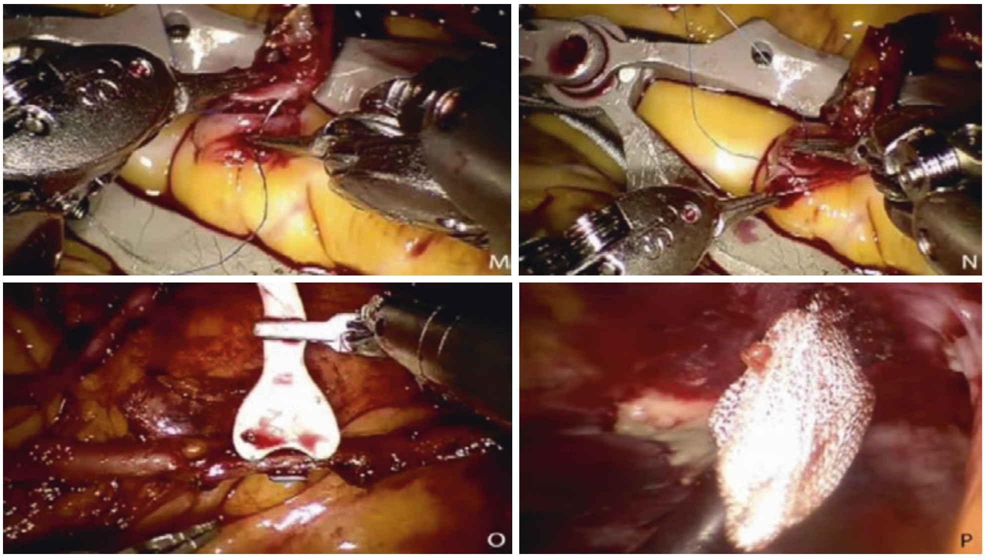
Fig. 18.1 (continued)



Cardiopulmonary Bypass and Myocardial Protection

Cardiopulmonary bypass is achieved through peripheral cannulation, most commonly via the left common femoral artery. Preoperative computed tomographic angiography of the chest, abdomen and pelvis is highly advised for planning consistently safe peripheral cannulation and cardiopulmonary bypass. Occult vascular pathology including hard and soft plaque, dissections, tortuous or small vessels, anatomic variations and other findings can lead to aortic dissection, malperfusion, cerebral vascular accident, aortic dissection and other major complications [5]. If such vascular pathology exists, an alternative cannulation site such as an axillary artery should be assessed or more technically demanding options such as direct aortic cannulation and an aortic crossclamp applied through the left chest could be considered. If these options are not feasible, beating heart TECAB may be an alternative, or traditional CABG should be undertaken.

Distal perfusion beyond the femoral arterial cannulation site is generally preferred to avoid potential leg ischemia, as a large cannula is usually required when using an endoaortic occlusion balloon. Perfusion beyond the arterial cannula can simply be achieved with a 6F sheath or similar cannula after gaining access through a separate purse string suture using a micropuncture kit. Alternatively, an 8 or 10 mm graft can be anastomosed to the femoral artery. Arterial cannulation is best performed using a perfusion cannula with a side arm through which an endoaortic occlusion balloon is passed over a guidewire into the aortic root. The tableside surgeon can carry out cannulation maneuvers, while the console surgeon harvests the IMAs.

After inflating the endoaortic occlusion balloon and ensuring proper position and stable bypass flow, cardioplegia is administered (Fig. 18.1f). A percutaneous pulmonary artery vent can provide a dry operative field and a percutaneous retrograde coronary sinus catheter can be considered to augment myocardial protection.

Surgical Procedure

Successful TECAB depends predominantly upon accurate port placement. After marking the midline of the sternum, port locations for the camera, right and left arms of the robot as well as the subxiphoid port are marked. The camera port is positioned lateral to the midpoint of the sternum where the chest begins to roll posteriorly, often one to two centimeters posterior to the anterior axillary line. Carbon dioxide is instilled into the thorax at approximately 7 mmHg to enhance working space. Communication with the anesthesiologist is required to maintain a stable hemodynamic profile. Right and left arm ports are placed 7–8 cm cranial and caudal and 2 cm medial to the camera port under endoscopic vision (Figs. 18.1b and 18.3).

After docking the robot, instruments are carefully introduced and the IMAs are harvested (Fig. 18.1c–e). Once completed, heparin is administered and the tableside surgeon establishes cardiopulmonary bypass. With enhanced working space, the stabilizer port is installed in the midclavicular line, about 2 cm caudal to the costal margin.

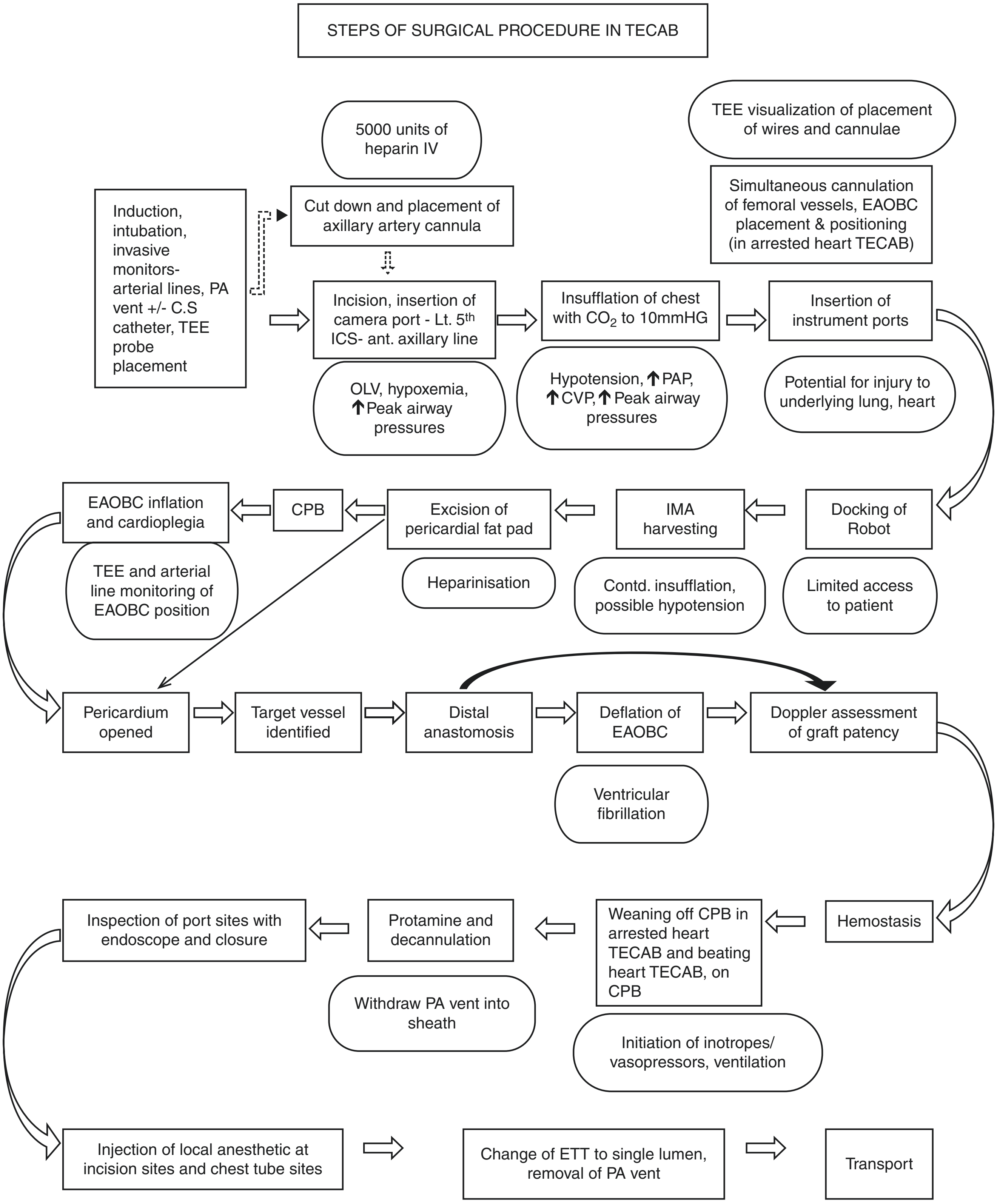

STEPS OF SURGICAL PROCEDURE IN TECAB
5000 units of heparin IV
TEE visualization of placement of wires and cannulae
Induction, intubation, invasive monitors- arterial lines, PA vent +/- C.S catheter, TEE probe placement
Cut down and placement of axillary artery cannula
Simultaneous cannulation of femoral vessels, EAOBC placement & positioning (in arrested heart TECAB)
Incision, insertion of camera port - Lt. 5th ICS- ant. axillary line
Insufflation of chest with CO_2 to 10mmHG
Insertion of instrument ports
OLV, hypoxemia, ↑Peak airway pressures
Hypotension, ↑PAP, ↑CVP, ↑Peak airway pressures
Potential for injury to underlying lung, heart
EAOBC inflation and cardioplegia
CPB
Excision of pericardial fat pad
IMA harvesting
Docking of Robot
TEE and arterial line monitoring of EAOBC position
Heparinisation
Contd. insufflation, possible hypotension
Limited access to patient
Pericardium opened
Target vessel identified
Distal anastomosis
Deflation of EAOBC
Doppler assessment of graft patency
Ventricular fibrillation
Inspection of port sites with endoscope and closure
Protamine and decannulation
Weaning off CPB in arrested heart TECAB and beating heart TECAB, on CPB
Hemostasis
Withdraw PA vent into sheath
Initiation of inotropes/ vasopressors, ventilation
Injection of local anesthetic at incision sites and chest tube sites
Change of ETT to single lumen, removal of PA vent
Transport

Fig. 18.2 Major procedural steps in performing totally endoscopic coronary artery bypass grafting. Main events—rectangular boxes, anesthetic implications/interventions of note—oval boxes, bold arrows—sequence of steps in beating heart TECAB, dashed arrows—possible alternative sequence of steps, CO_2 carbon dioxide, *CPB* cardiopulmonary bypass, *CS* coronary sinus, *CVP* central venous pressure, *DLT* double-lumen tube, *EAOBC* endoaortic occlusion balloon catheter, *ETT* endotracheal tube, *ICS* intercostal space, *IMA* internal mammary artery, *OLV* one-lung ventilation, *PA* pulmonary artery, *PAP* pulmonary artery pressure, *TECAB* totally endoscopic coronary artery bypass, *TEE* transesophageal echocardiography. (Modified from Deshpande et al. [3])

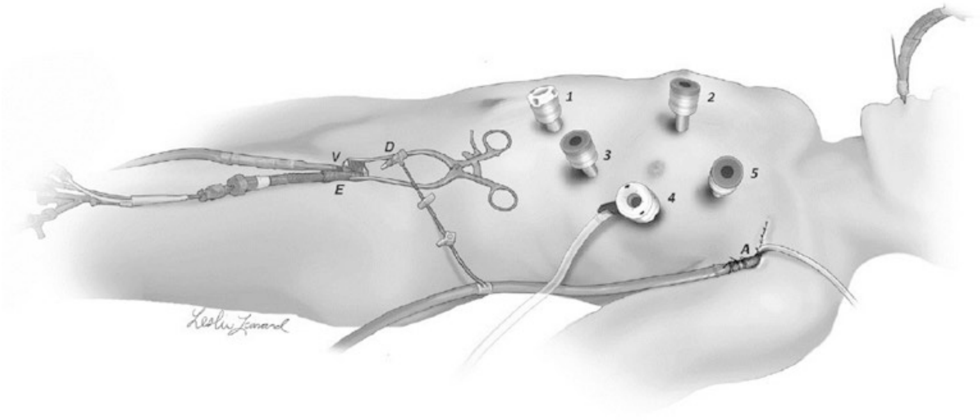


Fig. 18.3 Port sites and cannulation strategy for arrested heart totally endoscopic coronary artery bypass grafting. 1—subxiphoid port, 2—assistant port, 3—left robotic arm, 4–12 mm camera port, 5—right robotic arm, A—left axillary arterial cannulation site, D—distal left femoral artery perfusion, V—open left femoral venous cannulation, E—19 mm cannula in left femoral artery for endoaortic occlusion balloon. (Modified from Deshpande et al. [3])

A small window is made in the pericardium posterior to the left phrenic nerve to provide drainage of blood that may collect in the pericardium and obscure the operative field. Once the heart is arrested, the pericardial fat pad is dissected from medial to lateral, allowing it to hang laterally, which will hold the pericardium out of the operative field. A pericardiotomy is then made in a similar fashion as the dissection of the fat pad, taking care to avoid the phrenic nerve and the left atrial appendage (Fig. 18.1g).

Target vessels are identified after introducing the stabilizer and rotating the heart to visualize the appropriate coronary arteries. The coronary angiogram can be brought in picture-in-picture to the robotic console to aid in target vessel identification (Fig. 18.1h). Grafting is then carried out. After dissecting the target vessel with Potts scissors, a lancet blade is used to create an arteriotomy that is extended with scissors. The distal end of the graft is prepared and flow assessed. Anastomoses are created starting at the 2 o'clock position, moving clockwise around the back of the anastomosis working inside-out on the graft and outside-in on the target. Once around the heel of the anastomosis, it is probed. With the second arm of the 7 cm 7-0 Pronova suture (Ethicon, Cincinnati, OH) the anastomosis is completed working counterclockwise, outside-in on the graft and inside-out on the target vessel (Fig. 18.1i–n). Additional technical details describing performance of the coronary anastomosis are described in other presentations [5]. Graft length, position and flow are assessed and the patient is weaned from cardiopulmonary bypass (Fig. 18.1o). Full details of the procedure can be seen in our previously published video of a double vessel arrested heart TECAB [6].

Sternal sparing multi-arterial coronary artery grafting can be undertaken using a combination of bilateral IMAs, radial artery and saphenous vein grafts in single, sequential and Y-graft configurations. Y-grafts are best constructed intracorporeally prior to opening the pericardium, using the endostabilizer as a platform. Vein grafts can be attached to the left subclavian artery [7] and brought through the chest wall. These techniques have facilitated triple and quadruple [1] vessel coronary artery bypass procedures.

Beating Heart TECAB

TECAB is well suited for off-pump coronary revascularization. As with open off pump CABG, additional considerations are important to maintain hemodynamic stability. With the heart full and beating, working space is reduced. Again, open communication between the surgical and anesthesia teams is critical to maintain stable hemodynamics. Interventions by the anesthesiologist without discussion with the surgical team can lead to cardiac trauma. A lidocaine infusion can prevent or stabilize ventricular arrhythmias. Positive airway pressure on the deflated lung may enhance oxygenation without obscuring the surgical field. Transthoracic echocardiography throughout the procedure can monitor cardiac function and guide pharmacologic interventions to minimize changes in contractility and heart rate that can make suturing on the beating heart more challenging. Patient positioning and port placement is as for arrested heart TECAB. Additional details regarding technical aspects of performing a coronary anastomosis in an off pump TECAB are provided in detail in the surgical literature [8, 9].

An alternative to a hand-sewn anastomosis is the use of an anastomotic connector. Although not having gained widespread adoption in open CABG, the Flex A™ device constructs reproducible anastomoses [10] and has several advantages in beating heart TECAB that can simplify the operation. Anesthesia, positioning and other preliminary steps proceed as for sutured TECAB procedures. Skeletonized IMA harvesting allows for construction of Y-grafts and simplifies intrathoracic loading of the graft onto the anastomotic device.

Once the epicardium is dissected, a silastic snare is placed around the artery and a polytetrafluoroethylene CV8 horizontal mattress suture is placed in the adventitia a few millimeters proximal to the location of the anastomosis. Prior to installing the Flex A™ device, the robotic instruments are temporarily removed as there can be a reduction of the pressurized capnothorax, causing the heart and lungs to move towards the chest wall. The Flex A™ device is introduced through a 15 mm port in the second left intercostal space in the midclavicular line with the cartridge and anvil gently approximated and the other robotic instruments are again brought into the thorax. Next, the graft is loaded onto the device and with the robotic stabilizer exposing the target vessel; a 1 mm arteriotomy is made through the previously placed horizontal mattress suture. Grasping the Flex A™ device by a tab, the anvil is advanced through the arteriotomy at a 45° angle, oriented parallel to the target vessel and advanced to the tissue stop. Obviously, the anvil must clearly be intraluminal. The tableside surgeon fires the connector, and with caution to avoid disrupting the anastomosis, the device is removed, the anvil stitch is tied and the anastomosis is inspected. Additional grafts are completed in a similar fashion as required. Y-grafts can similarly be constructed. Further details on the use of an anastomotic connector endoscopically have been well described elsewhere [11].

Hybrid Revascularization

Hybrid coronary revascularization (HCR) combines the benefits of IMA grafts and percutaneous coronary intervention (PCI) to provide a patient specific coronary revascularization plan. In this fashion, complex coronary disease can be treated while preserving the sternum. Several approaches to HCR exist including simultaneous TECAB and PCI, TECAB first and PCI first. Surgery prior to PCI is often preferred to avoid operating on patients treated with dual antiplatelet therapy, but the order of interventions must be dictated by the coronary anatomy and severity of stenoses [12]. A meta-analysis demonstrated that drug-eluting stents were used in nearly 90% of HCR cases. Bare metal stents, angioplasty and thrombo-aspiration were employed in the remaining cases [13].

Hybrid revascularization techniques can be effective with low morbidity and mortality. Bonaros et al. reported no mortality, 3% myocardial infarction, and a less than 1% stroke. Sequence of the interventions did not affect the outcomes [14, 15]. A meta-analysis by Harskamp et al. suggested that HCR was associated with fewer blood transfusions, a shorter length of stay, and faster return to work [16]. It is important to consider that patients in these studies were highly selected; nevertheless, HCR can provide excellent outcomes to carefully selected patients with multi-vessel disease.

Learning Curve

Robotic TECAB is a complex surgical procedure and requires an intentional and iterative process to develop a successful program. All groups in the hospital must be dedicated to the success of the program, including administration, nursing, anesthesia, perfusion, surgical staff etc. A critiqued, outcomes-centered stepwise approach is important, beginning with LIMA harvesting, followed by pericardiectomy, and finally LIMA-LAD anastomosis. Cannulation techniques should be learned independent of the robotic steps during otherwise conventional operations. Each step should be mastered before moving forward with other portions of the operation. Robotic LIMA-LAD via sternotomy can also be considered to eliminate learning this step intracorporeally [17–19]. The learning curve is substantial; although there is a rapid decline in time to complete procedure steps after 20 cases, marginal gains continue to be obtained and can be documented even after 100 cases [18] (Fig. 18.4). Once a single vessel TECAB has been mastered, more complex procedures including multi-vessel TECAB can be added. Experience can also be attained by first performing robotic assisted coronary artery bypass. The LIMA is harvested robotically and after exposing the target vessel, the anastomosis is completed via mini-thoracotomy.

Patient selection is critical in developing a successful robotic coronary program and can change with program experience. Exclusion criteria often include patients with severely reduced left ventricular ejection fraction (<30%), small distal coronary vessels (less than 1.5 mm), previous left lung trauma or surgery, prior sternotomy, lung disease precluding single lung ventilation and emergent procedures. Patients with multiple comorbidities predicting poor physiological reserve should also be avoided [19]. Bonatti and others have reported that a consistent operative team, use of fibrin glue at the anastomosis, and a fourth endoscopic port for a tableside assistance improves the learning curve [18–20]. It is also important to consider early conversion to sternotomy if there are intraoperative challenges, as outcomes tend to be inferior as operative times become prolonged [21].

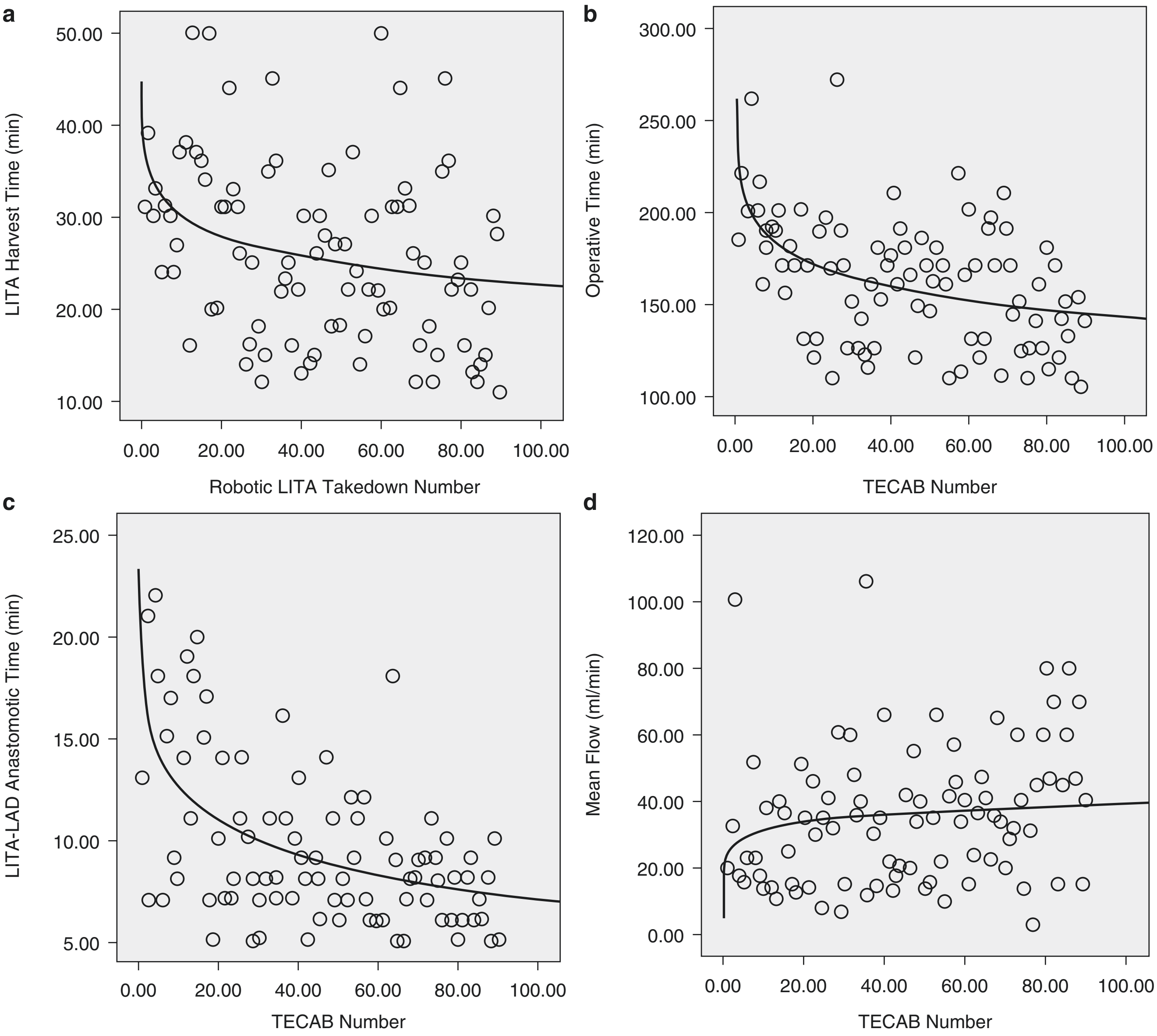


Fig. 18.4 Analysis of left internal mammary artery harvest time (**a**) operative time (**b**) anastomotic time (**c**) and mean graft flow (**d**) demonstrates a steep learning curve in the first 20 cases of totally endoscopic coronary artery bypass grafting. Incremental improvements continue beyond 100 cases. (Modified from Cheng et al. [18])

Outcomes

Robotic applications in CABG continue to develop. Feasibility of TECAB was demonstrated 20 years ago [21], but acceptance has been limited. Highly specialized centers across the world continue to advance the field and assess safety and efficacy of the procedure in various populations. Indeed, TECAB has become standard therapy in several hospitals across the world. With experience, conversion rates to open operation drop to less than 10% [22, 23]. Reasons for intraoperative conversion include LIMA injuries (2% or less), poor graft flow and anastomotic bleeding [23]. Other reasons include adhesions and physiologic intolerance. Return to the operating room for early complications occurs in the 1–2% range, which is in keeping with open CABG, and is typically secondary to bleeding [2]. Cardiopulmonary bypass time has generally been prolonged, averaging between 110–120 min for TECAB, where as conventional cases, tend to take just over half that time. Cross-clamp times are also approximately twice as long in some reports for robotic procedures as for open cases [24].

Table 18.2 Discharge, short-, mid-, and long-term angiographic/computed tomography angiography follow-up results of left internal mammary artery graft patency with Fitzgibbon grade for TECAB

	30 days	6 months to 1 year	1–3 years	3–5 years
Follow up	100	84	46	35
Fitzgibbon A	100	82	44	34
Fitzgibbon B	0	1	1	0
Fitzgibbon O	0	1	1	1
Graft patency	100%	98.8%	97.8%	97.1%

TECAB totally endoscopic coronary artery bypass grafting. (Modified from Yang et al. [24])

Outcomes for TECAB have been satisfactory. Postoperative myocardial infarction, stroke and mortality are similar to standard CABG [22, 23]. In 500 consecutive cases, there were five deaths (1%) cases and a low incidence of new onset atrial fibrillation (15%) [17]. A propensity score analysis showed that hospital and intensive care unit length of stay were comparable to conventional approaches [24], however, a prospective study by Leyvi indicated that discharge to an acute care facility was significantly lower in TECAB (16.0% vs. 25.83%, p = 0.008) [25].

Graft patency after TECAB exceeds 95% at three-year follow-up [2]. Three-month angiography on 76 patients identified graft occlusion in two cases and significant anastomotic stenosis in four cases. In addition one patient case required re-intervention on post-operative day one for graft occlusion. Of the six that were observed at three month follow-up, only one patient was symptomatic and only one required re-intervention [23]. Long-term graft patency also appears favorable. Using conventional angiography or computed tomographic angiography, 34 of 35 (97.1%) of grafts were patent at 3–5 years (Table 18.2) [25].

Functional recovery after TECAB is generally rapid as the sternum is not divided. Median time to walking outside the home was 1 week, resumption of household work was 2 weeks, resumption of driving was 3 weeks and patients resumed sporting activities or biking at 6 weeks [26].

Conclusion

TECAB has proven to be a safe and efficacious method of coronary revascularization with sparing of the sternum, minimizing the risk of sternal wound infection and blood loss while affording patients faster return to normal activity. The cost of these benefits is increased CPB and total operative time. Current literature supports the safety and efficacy of the technique in properly selected patients. Deliberate practice and collective experience will continue to refine the procedure and allow more patients to benefit from TECAB.

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Redo Coronary Artery Bypass Grafting

19

Hitoshi Yaku, Sachiko Yamazaki, and Satoshi Numata

High Yield Facts

- The number of redo coronary artery bypass grafting (CABG) procedures is on the decline.
- Early surgical outcomes of redo CABG, although improving, are worse than that of primary CABG.
- Long-term outcomes are comparable between redo and primary CABG after adjusting early risks.
- Off-pump redo CABG has better early surgical outcomes than on-pump CABG.
- Repeat median sternotomy sparing approaches are a promising alternative to reduce surgical risks.

Table 19.1 Challenges in redo coronary artery bypass grafting

• Patient's condition
Older
Co-existing disease (PAD)
Atheromatous disease in the native coronary arteries and grafts
Decreased ventricular function
• Frequent urgent operation
• Sternal reentry
• Presence of patent arterial grafts and adhesions
• Myocardial protection
• Lack of conduits

PAD peripheral arterial disease

Introduction

Redo coronary artery bypass grafting (CABG) is a more demanding procedure than primary CABG [1]. This is primarily due to the increasing age of the patients with increasing co-morbidities, atheromatous disease in the native coronary arteries and grafts, and decreased ventricular function. Additionally, patients frequently need urgent surgery; sternal re-entry is sometimes dangerous if the adjacent structures, including the ascending aorta, patent grafts, or right ventricle are adherent to the back of the sternum; there is a risk of coronary embolism while dissecting the heart with diseased patent grafts; myocardial protection is difficult if some of the ventricular area is perfused only by patent in-situ grafts; and finally, there are sometimes no good quality conduits (Table 19.1). However, there have been recent improvements in surgical strategy and techniques making redo CABG a much safer procedure.

Recent Trends

The number of redo CABGs has decreased by half over the last 10 years in Japan (Fig. 19.1). Redo CABG now constitute less than 2% of total isolated CABG. Aggressive percutaneous coronary intervention (PCI) especially for patients with previous CABG, even in diseased vein grafts, and the fact that patients more frequently have arterial grafts at the primary operation are predominant reasons for the decline in redo CABG procedures. Figure 19.1 also shows that off-pump redo CABG is performed in about half of the patients requiring redo CABG in Japan [2].

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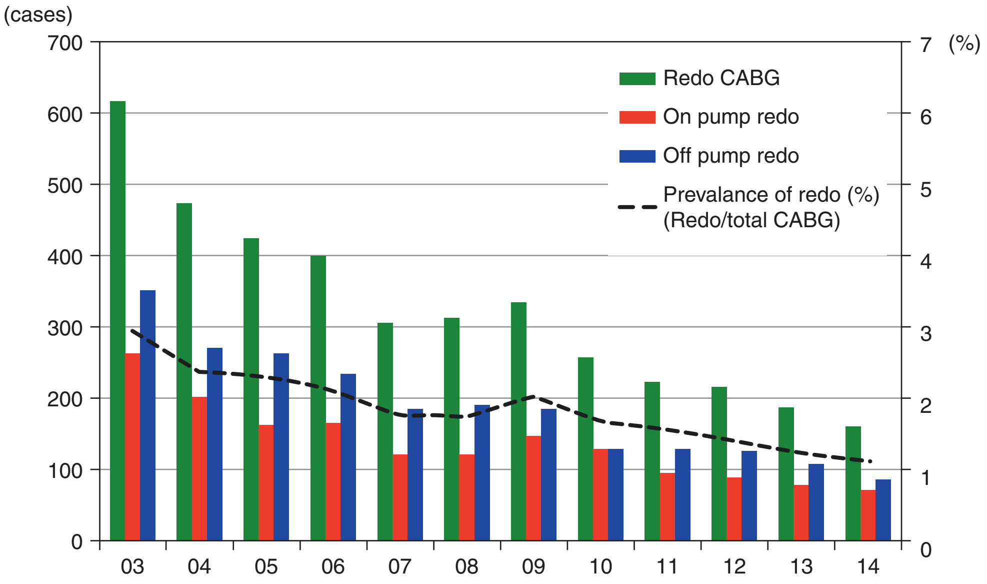


Fig. 19.1 Status of redo coronary artery bypass grafting in Japan (2003–2014). Reproduced with permission from [2]

Indications

According to the latest European guidelines [3], the optimal treatment strategy in patients with acute graft failure should be decided by *ad hoc* consultation between the cardiovascular surgeon and the interventional cardiologist, on the basis of the patient's clinical condition and the extent of myocardium at risk (Class I Level C). In the case of early post-operative graft failure, emergency *ad hoc* PCI may limit the extent of infarction, if technically feasible. The target for PCI is the native vessel or the ITA graft, while the acutely occluded saphenous vein graft (SVG) and any anastomotic site should be avoided, if possible, due to concerns regarding embolization or perforation. Redo surgery should be favoured if the anatomy is unsuitable for PCI, if several important grafts are occluded, or in the case of clear anastomotic errors. In asymptomatic patients, repeat revascularization should be considered if the artery is of an appropriate size and supplies a large territory of myocardium.

In case of disease progression and late graft failure, repeat revascularization in these patients is indicated in the presence of significant symptoms despite medical treatment (Class I Level B), and in asymptomatic patients with objective evidence of large myocardial ischaemia (>10% of the left ventricle) [3]. If considered safe, PCI should be considered as first choice over CABG (Class IIa Level B).

If the patient has stenotic vein grafts, some factors influencing the selection of either CABG or PCI are shown in Table 19.2.

Table 19.2 Indications for redo CABG and PCI when saphenous vein grafts are stenotic

Redo CABG better	PCI better
Late (>5 years) stenosis	Early (<5 years) stenosis
Multiple stenotic vein grafts	Single stenotic vein graft
Diffusely atherosclerotic vein grafts	Other patent vein grafts
Stenotic LAD vein graft	Focal graft lesions
No patent ITA graft	Patent ITA–LAD graft
Abnormal left ventricular function	Normal left ventricular function

CABG coronary artery bypass grafting, *ITA* internal thoracic artery, *LAD* left anterior descending artery, *PCI* percutaneous coronary intervention

Technical Considerations

Sternal Re-entry

Most redo CABGs are performed through the same median sternotomy as the primary operation. The wires are cut anteriorly but not removed. The sternum is cut with an oscillating saw, while the wires are pulled up, and the tissue beneath the sternum is away from the sternum. It is better to use a micro-oscillator saw, because it conveys the sensation of cutting the inner layer of the sternum (Fig. 19.2). We recommend to cut the whole outer layer and the inner layer without periosteum with a micro-oscillator saw, and then cut the periosteum with scissors.

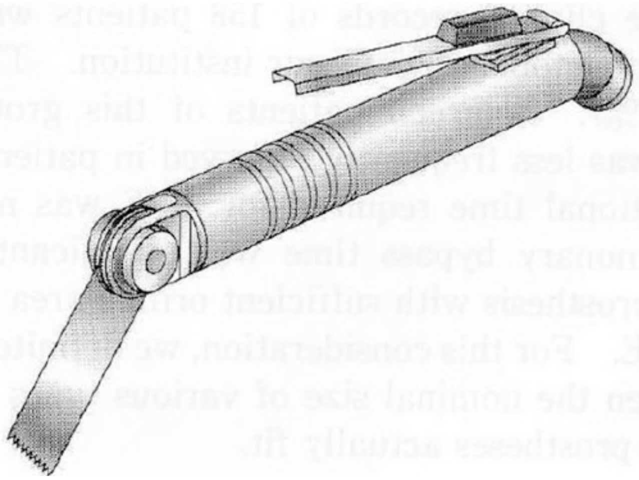


Fig. 19.2 Micro-oscillator saw

If a patent ITA graft or the ascending aorta is adherent to the back of the sternum, an anterior thoracotomy near the adhesion is made, and dissection of the adhesion is performed, and repeat median sternotomy is performed. If dissection of the adhesion is considered difficult, peripheral cannulation is performed in the groin, body temperature is cooled to prepare for circulatory arrest in case the patent vital graft or the ascending aorta is injured. If some aortic regurgitation is present, left ventricular venting is required to prevent overdistension of the left ventricle while cooling the heart. We insert a vent directly from the apex of the left ventricle via a small left thoracotomy [4]. Multidetector computed tomographic angiography is mandatory for detection of adhesion of the adjacent structures, including the ascending aorta, patent grafts, or the right ventricle to the back of the sternum [5].

Dissection of the Heart, Ascending Aorta and Grafts

Once the sternum is safely re-entered, dissection of the heart is started adjacent to the diaphragm. Dissection is relatively easy at the pericardium on the diaphragm. Dissecting the aortic and venous cannulation sites in the early stage of the operation is important to initiate cardiopulmonary bypass at any time if needed.

If redo CABG is performed in a conventional fashion (using cardiopulmonary bypass with the heart arrested by cardioplegia), cardiopulmonary bypass can be started at this point, and further dissection can be performed with the heart decompressed on cardiopulmonary bypass.

When performing off-pump redo CABG, it is important to create slack on the right-sided pericardium in order to prevent the pericardium from compressing the heart while rotating it. To this end, we incise the pericardium on the diaphragm and at the reflection of the superior vena cava, leaving the pleura intact, if possible. Dissection is proceeded from the right ventricle to the left ventricle. Once the apex is dissected, a heart positioner that is used in off-pump CABG, is applied to the apex, the heart is rotated to the right and dissection of the lateral wall of the left ventricle is performed. A harmonic scalpel is useful and safe to dissect the heart [6].

Dissection of the diseased vein grafts should be minimized; they are just dissected free from the pericardium. On the other hand, the patent ITA should be dissected free for almost its whole length, because the ITA must be clamped while the heart is arrested in conventional redo CABG. On the other hand, in redo off-pump CABG, one cannot rotate the heart without ITA dissection. If the right ITA was used to connect to the LAD across the midline, it must be dissected free in order to secure the aortic cannulation and cross-clamp sites. To dissect the patent ITA graft, the use of a harmonic scalpel is strongly recommended. The blade of the harmonic scalpel is never heated to above 80 °C and never causes thermal injury to the ITA, provided it is used properly. When the circumflex artery is to be grafted, the lateral wall of the left ventricle should be dissected up to the left pulmonary vein.

Alternative Approaches to Repeat Median Sternotomy

The other approaches for grafting are transabdominal approach and posterolateral thoracotomy approach. Glineur et al. [7] performed redo CABG using a pedicled right gastroepiploic artery (RGEA) in 15 patients. Off-pump grafting of the pedicled RGEA was targeted at the posterior descending artery in 14 patients and at the LAD artery in one patient. Thirty-day mortality was 6.5% (one patient) and one graft was occluded. Tavilla and Bruggemans [8] performed redo CABG off-pump using RGEA grafted to the inferior wall of the heart using a transabdominal approach. There was no in-hospital mortality, and the estimated freedom from major cardiovascular and cerebrovascular event rate was 70.2% at 6 years. Azoury et al. [9] performed redo CABG to the circumflex system via posterolateral thoracotomy with no hospital mortality. These alternative approaches to repeat median sternotomy appear to be effective and safe for patients with patent grafts, especially ITA to the LAD artery.

Cardioprotection

Cardioprotection is extremely important, especially in redo CABG, because the coronary arteries of patients undergoing redo CABG are often severely atherosclerotic, and totally occluded. Care should be taken to protect myocardium, especially if it is mainly perfused by the ITA. In such a case, cardioplegic solution should be given, not only from the root of the ascending aorta in an antegrade fashion, but also from the coronary sinus in a retrograde fashion [10, 11].

Grafting Pattern and Selection of Conduits

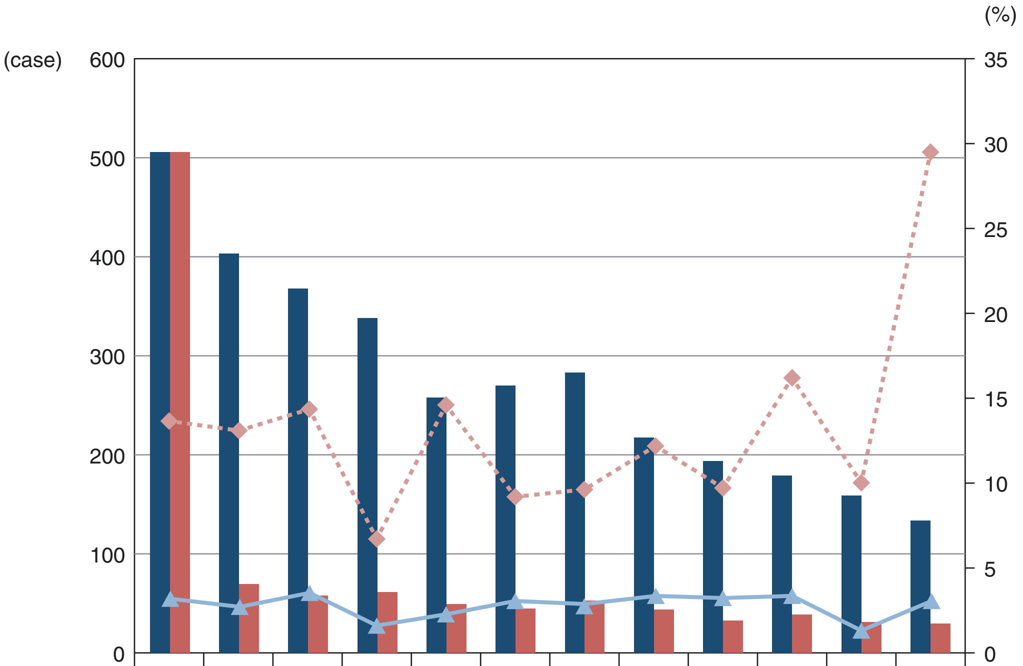
One of the difficulties in performing redo CABG is the selection of bypass conduits. The basic concept of how to select bypass conduits in redo CABG is the same as that in primary CABG. If only the saphenous vein was used in a primary CABG, the left and right ITAs are available for redo CABG. Many patients who undergo redo CABG may have a patent ITA-to-LAD graft, whereas SVGs to the right and left circumflex arteries are occluded. In such a case, both bypass grafts to the right and circumflex arteries can be replaced by new SVGs; other choices of grafts are the right ITA and the radial arteries.

Even in redo CABG, we have to try to use an ideal grafting pattern. If the LAD needs to be grafted, the ITA should be used. If the left ITA-LAD graft is patent and the left circumflex artery needs to be grafted, the right ITA is the choice because the bilateral use of ITA has a survival benefit over the single use of ITA [12, 13]. When the right ITA is used as an in situ graft, it can be used to the circumflex arteries via the transverse sinus; however, dissection of the sinus may be difficult in a redo situation. In such cases, the right ITA can be used as a free graft from the ascending aorta or from the body of the left ITA making a composite graft. Another option is to exchange the left ITA-to-LAD graft to the circumflex artery, whereupon the in situ right ITA is used for the LAD. In this way, the single ITA graft arrangement can be upgraded to a bilateral ITA graft arrangement [14].

The RGEA can be a good option for a graft to the inferior wall in redo CABG. When the inferior wall is the only target in redo CABG, grafting using the in situ RGEA through the diaphragm is possible in an off-pump fashion [7, 8].

Surgical Outcomes

Sabik et al. [1] reported that the surgical outcome of redo CABG in terms of hospital mortality has been improving; however, it remains three times higher than that of primary CABG. The operative mortality of redo CABG has fluctuated, not improved, while the operative mortality of primary CABG has been gradually but steadily decreasing. Figure 19.3 shows the proportion of elective and emergent cases in redo CABG. The number of emergent cases has not been decreasing, whereas the number of elective cases has dramatically



	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
🟦 Redo, elective (n)	507	405	369	338	257	269	283	217	192	179	158	133
🟥 Redo, emergency (n)	110	69	56	60	48	44	52	41	31	37	30	27
▲ 30-day mortality elective (%)	3.16	2.72	3.52	1.48	2.24	2.97	2.83	3.23	3.12	3.35	1.27	3.01
◆ 30-day mortality emergency (%)	13.64	13.04	14.29	6.67	14.58	9.09	9.62	12.20	9.68	16.21	10.00	29.36

Fig. 19.3 The number and operative mortality of elective and emergent redo coronary artery bypass grafting in Japan (2003–2014). Reproduced with permission from [2]

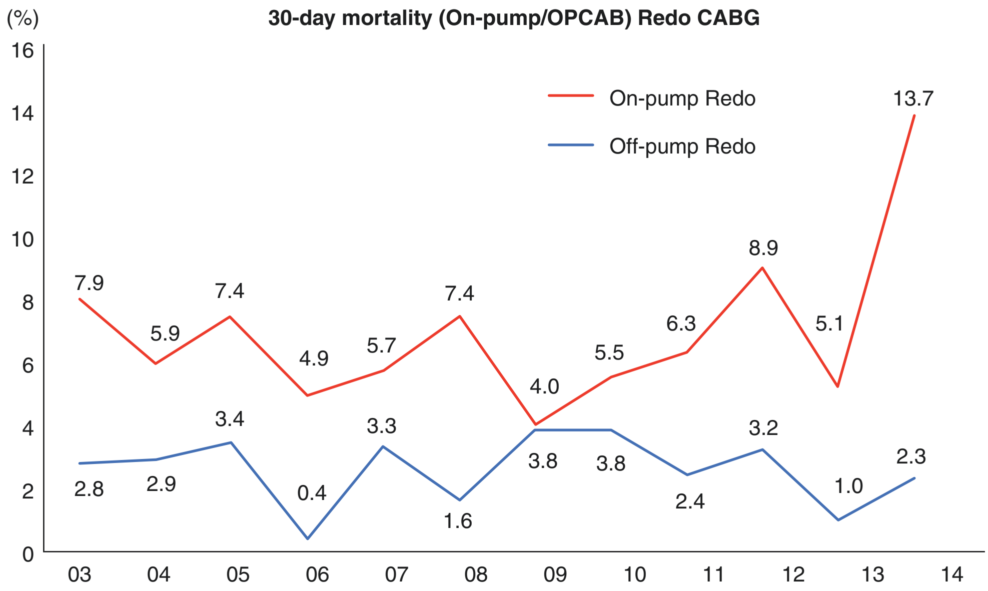


Fig. 19.4 Operative mortality of on-pump and off-pump redo coronary artery bypass grafting in Japan (2003–2014). Reproduced with permission from [2]

decreased. The operative mortality in emergent cases has been very high, with an exceptionally high number in 2014. Figure 19.4 shows the comparison of operative mortality between off-pump and on-pump strategies in redo CABG. The operative mortality in off-pump redo CABG has been always better than that of on-pump. In 2014, the operative mortality of patients who required emergent surgery with cardiopulmonary bypass probably due to hemodynamic instability was extremely high.

Yap et al. [15] reported Kaplan-Meier curves of 5-year survival in primary and redo CABG. The 5-year survival curve of redo CABG was significantly lower than that of primary CABG; however, when the initial drop of the survival was adjusted, the two curves were superimposable. This fact may indicate that once the higher operative mortality in redo CABG could be reduced, redo CABG would have the same impact on the patient survival as that of primary CABG.

Maltais et al. [16] from Mayo Clinic reported their 20-year experience of redo CABG. The median age of the patients was 69 years. All 748 patients underwent on-pump CABG with 6% operative mortality. The early nonfatal morbidity rate, including renal failure, was 7%, and the incidence of stroke was 6%. Overall 1-, 5-, and 10-year survival was 89%, 77%, and 51%, respectively. Risk factors affecting long-term survival were age, diabetes, peripheral vascular disease, and end-stage renal disease with dialysis, whereas higher LV ejection fraction had protective effects.

PCI vs CABG for Repeat Revascularization

Cole et al. [17] reported short-term and long-term outcomes of PCI or CABG for diabetic patients who had CABG previously. In-hospital mortality was greater for redo CABG than for PCI (11.2% vs 1.61%; $P < 0.0001$). However, long-term survival was comparable for redo CABG and PCI (5-year survival; 61% vs 62%, 10-year survival; 26% vs 32%, log-rank test $P = 0.14$). An additional revascularization with CABG was more common in patients initially treated with PCI. The strongest risk factor for in-hospital mortality was coronary surgery, with OR of 6.51. Other correlates included year of the revascularisation procedure, age, gender, and lower left ventricular ejection fraction. The factors that correlated with long-term mortality included age, gender, left ventricular ejection fraction, and hypertension. Interestingly, Class III–IV congestive heart failure significantly correlated with long-term mortality for patients with PCI (HR 1.54, 95% CI 1.25–1.89) but not for patients treated with CABG (HR 1.19, 95% CI 0.97–1.45). Evidence that CABG offers better outcomes than does PCI for primary revascularization procedures in diabetic patients with multivessel disease [18, 19] cannot be generalised to diabetic patients with previous CABG, except for patients with severe heart failure.

In the Angina With Extremely Serious Operative Mortality Evaluation (AWESOME) randomized trial and prospective registry [20], there were 142 patients who had previous CABG among 454 patients in the randomized trial, 719 patients with previous CABG among 1650 patients in the physician-directed registry, and 119 patients with previous CABG among 327 patients in the patient-choice registry. Three-year survival of redo CABG and PCI were 73% and 76%, respectively, in the randomized trial (log-rank = NS), 71% and 77%, respectively in the physician-directed registry (log-rank = NS), 65% and 86%, respectively, in the patient-choice registry (log-rank test $P = 0.01$).

In the situation of acute perioperative graft failure following CABG, Thielmann et al. [21] investigated whether emergency PCI, emergency operation, or conservative intensive care treatment should be applied. Among 5427 consecutive isolated CABG patients, 118 underwent emergency coronary angiography because of evidence of perioperative myocardial infarction. Angiography revealed early bypass graft failure in 67 among 118 patients and 84 among 214 bypass grafts after CABG. Emergency PCI was performed in 25 patients, redo CABG in 15 patients, and conservative treatment in 27 patients. In-hospital and 1-year mortality were 12.0% and 20.0%, respectively, in patients with emergency PCI, 20.0% and 27.0%, respectively, in patients with emergency redo CABG, and 14.8% and 18.5%, respectively, in patients with conservative treatment. The authors concluded that emergent PCI may limit the extent of myocardial cellular damage more so than the surgical-based treatment strategy of patients with acute perioperative myocardial ischaemia due to graft failure following CABG.

Off-Pump vs On-Pump Redo CABG

As mentioned in the previous section, if the worse early outcomes of redo CABG could be overcome, one can achieve comparable long-term outcome compared to primary CABG. To improve early surgical outcome by eliminating adverse effects of cardiopulmonary bypass, off-pump CABG may be an effective procedure, even in redo CABG. Using the national database in Japan, Dohi et al. [22] reported that between 2008 and 2011, redo CABG was performed in 619 patients (1.8%) among 34,980 patients who underwent isolated CABG. Of the 619 patients who underwent redo CABG, 364 patients (69%) had off-pump CABG. After risk adjustment of baseline characteristics by propensity score matching with 13 preoperative risk factors, patients undergoing redo off-pump CABG had lower 30-day mortality rate (3.3% vs 7.0%, $P = 0.18$), a significantly lower rate of composite mortality or major morbidities (11.0% vs 21.5%, $P = 0.006$), a significantly lower rate of prolonged ventilation (>24 h) (7.0% vs 15%, $P = 0.0016$), a significantly shorter duration of ICU stay (≥8 days) (7.0% vs 14.5%, $P = 0.023$) and a significantly decreased need for transfusion (71.5% vs 94.0%, $P < 0.0001$) than patients undergoing on-pump redo CABG.

Bruno et al. [23] compared early and 10-year surgical outcome between off-pump and on-pump CABG. They reported that 84 patients undergoing redo off-pump CABG had lower composite of in-hospital mortality, acute kidney injury, stroke and severe low cardiac output requiring intra-aortic balloon pump (8% vs 19%, $P = 0.004$), less in-hospital mortality (0% vs 5%, $P = 0.13$), and 4.5 times less need for intra-aortic balloon pump (2% vs 11%, $P = 0.002$) compared to redo on-pump CABG. Ten-year survivals were comparable for off-pump and on-pump redo CABG (71.6% vs 71.7%, log-rank test: $P = 0.61$).

Shin et al. [24] also reported that off-pump redo CABG had a lower rate of early complications (33.3% vs 64.2%, $P = 0.082$), and statistically comparable hospital mortality (0% vs 7.1%, $P = 0.249$). There was no significant difference in the 10-year survival rate between off-pump and on-pump redo CABG (100% vs 79.6%, $P = 0.225$).

Mack [25] performed redo CABG in 87 consecutive patients on an intent-to-treat basis without cardiopulmonary bypass. Ninety-four percent procedures were successfully completed off-pump (conversion rate: 5.8%). Seventy-eight percent of the patients had a repeat median sternotomy approach and 22% underwent a limited anterior or lateral thoracotomy. The operative mortality was 2 of 86, and no mortality occurred among the conversion patients. In addition, no strokes or perioperative myocardial infarctions occurred.

According to these previous studies, off-pump redo CABG may have a potential to reduce early surgical risk, while maintaining long-term survival. Therefore, the off-pump technique may be a procedure of choice whenever possible in redo CABG.

Summary

Redo CABG is a challenging procedure. All aspects are worse than those of primary CABG. Furthermore, in-hospital mortality with redo CABG is higher than that with primary CABG or PCI. However, once patients survive the early surgical period, the effect of coronary revascularization by redo CABG appears to be the same as that of primary CABG and may be better than that of PCI. Therefore, the strategy of reducing operative risk of redo CABG is the key for performing redo CABG. The technical advances including retrograde cardioplegia, off-pump technique, use of arterial grafts, and alternative approaches to repeat median sternotomy may improve early and late surgical results for patients who require repeat coronary revascularization after CABG.

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Hybrid Coronary Revascularization

20

Elbert E. Williams, Gianluca Torregrossa,
and John D. Puskas

High Yield Facts

- Hybrid coronary revascularization consists of a planned combination of coronary artery bypass grafting and PCI to achieve full revascularization.
- Coronary artery bypass grafting in hybrid coronary revascularization involves minimally invasive approaches to graft the left internal thoracic artery to the left anterior descending. Hybrid revascularization often utilizes robotic techniques without manipulation of the ascending aorta to prevent major comorbidities such as stroke while still providing the long-term benefit of a left internal thoracic artery graft to the left anterior descending.
- Candidates for hybrid coronary revascularization must have coronary artery disease in the proximal or mid left anterior descending as well as at least one other non-left anterior descending artery with a moderate SYNTAX score.
- Existing data comparing multi-vessel PCI and hybrid coronary revascularization show similar freedom from major adverse cardiac and cerebrovascular events at 1 year. However, at 18 months, the hybrid coronary revascularization patients showed lower rates of major adverse events.

Introduction

Modern treatment of coronary artery disease (CAD) broadly divides into three treatment options, albeit with some overlap: medical therapy, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG). CABG has evolved over decades but remains the most commonly performed cardiac surgery with approximately 200,000 isolated cases annually in the United States [1]. Since 1968, when the first left internal thoracic artery (LITA) in the United States was sewn to the left anterior descending artery (LAD) by Dr. George Green in New York City, LITA grafting has been a vital component of CABG in the treatment of CAD [2]. Definitive clinical evidence supporting the use of the LITA as a bypass conduit appeared in the 1980s when the Cleveland Clinic reported that, compared to an all-vein graft strategy, LITA grafting was associated with improved survival, reduced risk of myocardial infarction and reduced need for repeat revascularization at 10-years follow-up in a large series of patients [3]. PCI, too, has evolved with improved techniques and stent materials, with newer generations of stents showing lower rates of restenosis and subsequent need for revascularization procedures [4].

As demonstrated in multiple trials (SYNTAX, FREEDOM, ASCERT), in patients with multivessel CAD, CABG is associated with superior long-term survival, more complete revascularization, improved long term relief from angina, and lower need for repeat revascularization when compared with PCI. However, PCI has lower rates of periprocedural stroke, blood transfusion, atrial fibrillation, and morbidity [5–7]. There is evidence to suggest that much of the improved survival seen in CABG is likely due to the LITA-to-LAD graft. The superiority of the LITA over a saphenous vein graft (SVG) or intracoronary stent is due to an intrinsic resistance to the development of atherosclerosis and the native production of nitrous oxide, promoting vasodilation of the entire downstream coronary circulation [8, 9].

Modern approaches to caring for patients with CAD seek the best long-term outcomes with the lowest possible risk. Hybrid coronary revascularization (HCR) offers the benefits of the LITA-to-LAD anastomosis coupled with the less invasive nature of PCI.

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Hybrid Coronary Revascularization

While the definition of HCR varies depending on the registry or guidelines referenced, HCR is comprised of a planned combination of CABG and PCI techniques to address multiple coronary lesions in concurrent or staged settings during a predetermined time interval, often during the same hospitalization. Specific to this chapter and in keeping to what is practiced in most centers, we will be discussing minimally invasive (non-sternotomy, off-pump) LITA-to-LAD CABG combined with PCI to non-LAD lesions.

Rationale for HCR

HCR combines the minimal invasiveness and safety of PCI with the most beneficial aspect of CABG, the LITA-to-LAD anastomosis. Essentially, HCR trades SVGs for stents to non-LAD lesions.

With minimally invasive surgical techniques, major morbidities of CABG are avoided. Cardiopulmonary bypass is avoided using off-pump CABG techniques to perform the LITA-to-LAD anastomosis and the risk of stroke can be sharply reduced given that aortic manipulation is completely avoided. Meta-analysis shows that anaortic off-pump CABG (as performed with HCR), has a 0.22 (0.14–0.33) odds ratio for stroke when compared with conventional CABG [10]. Furthermore, absolute rates of stroke have been reported as low as 0.09% with anaortic techniques [11]. With minimally invasive incisions, the pain and prolonged recovery intrinsic to sternotomy in traditional CABG are decreased.

Patient Selection

For a patient to be eligible for HCR, the patient needs to have CAD of his proximal or mid LAD as well as one other coronary lesion requiring revascularization. Typically, the lesion(s) for PCI need to be non-complex and of a lower SYNTAX score. Patients, too, must be eligible for minimally invasive CABG. While taking the patient's history, it is important to note any prior chest surgeries or intrathoracic infections that may result in dense pleural adhesions as these may preclude a robotic or mini-thoracotomy approach. Body habitus must also be taken into account. Although there are no absolute parameters, morbid obesity makes both minimally invasive LITA harvest and anastomosis more difficult. Furthermore, the patient must be able to tolerate single lung ventilation and a history of severe COPD or lung pathology may disqualify the patient from a minimally invasive, single lung ventilation approach. Careful angiographic evaluation to determine if the LAD is fit for a minimally invasive approach is essential. Relative contraindications are an intramyocardial LAD, heavy vessel calcification, or small vessel size. None of these are absolute contraindications but any of these findings deserve careful consideration by the heart team to determine if HCR is the appropriate approach. Finally, the patient must not have a contraindication to dual antiplatelet therapy postoperatively.

Additional reasons to consider HCR are if the patient has a high operative risk with conventional CABG or poor non-LAD bypass targets. HCR should not be considered for patients with hemodynamic instability or those in cardiogenic shock.

Surgical Approaches

MIDCAB

Minimally invasive direct coronary artery bypass grafting (MIDCAB) was first developed in the 1990s as described by Calafiore and Subramanian. This technique utilizes an anterolateral thoracotomy in combination with a specialized retractor that allows for the same incision to be used for both LITA harvest and the LITA-to-LAD anastomosis [12, 13].

Robotic Approaches

MIDCAB and other minimally invasive techniques gradually progressed to thoracoscopy, which in turn led to the use of robotics. With robotics, there are two major options: totally endoscopic coronary artery bypass grafting (TECAB) and robotic-assisted MIDCAB. Robotic-assisted MIDCAB consists of robotic harvest of the LITA through three small incisions paired with a small anterior thoracotomy through which the LITA-to-LAD anastomosis is performed under direct vision. TECAB, however, involves robotic harvest of the LITA and robotic anastomosis of the LITA-to-LAD with a closed chest. This robotic anastomosis can be done with running suture or with the aid of distal anastomotic stapling device [14]. In our institution, the most commonly used technique for HCR is robotic-assisted MIDCAB.

Technique

After placement of an arterial line and central line, as is standard for other cardiac procedures, either a dual-lumen endotracheal tube or a bronchial blocker must be placed. Robotic harvest of the LITA requires single lung ventilation in order to allow for instrumentation and visualization in the left chest.

Success of robotic LITA harvest is dependent on proper positioning and exposure of the left chest. First, external defibrillator pads must be placed as there will be limited access to the heart should fibrillation occur. The patient's chest must be brought to the leftmost edge of the operating table. A "bump" (rolled towel or silicon roll) is then placed under the left chest in a cranial-caudal orientation; the top of this roll should be caudal to the left scapula in order to let the left shoulder drop towards the floor, facilitating the arc of movement of the right robotic limb. The left arm is extended posteriorly and the elbow slightly flexed before it is padded and secured ensuring that the anterolateral left chest is completely exposed. Draping should ensure that the sternum is accessible should sternotomy become necessary (Fig. 20.1). Before any incisions are made, the left lung should be deflated using the bronchial blocker or dual-lumen endotracheal tube.

Port placement aims to triangulate the LITA while ensuring the robot arms will not be hindered by the patient's shoulder or arm. A Veress needle placed through the most cranial port site is used to begin CO_2 insufflation of the left chest. Care must be taken to monitor the blood pressure closely as it is possible to cause a tension pneumothorax. We routinely set the CO_2 insufflation at 12 mmHg and adjust higher or lower depending on visualization and blood pressure stability. After Veress needle insufflation, the middle camera port is placed under vision using an optical trocar and a laparoscopic camera. CO_2 insufflation is changed to that trocar as the Veress needle is removed. The remaining two robotic working trocars are placed under direct vision.

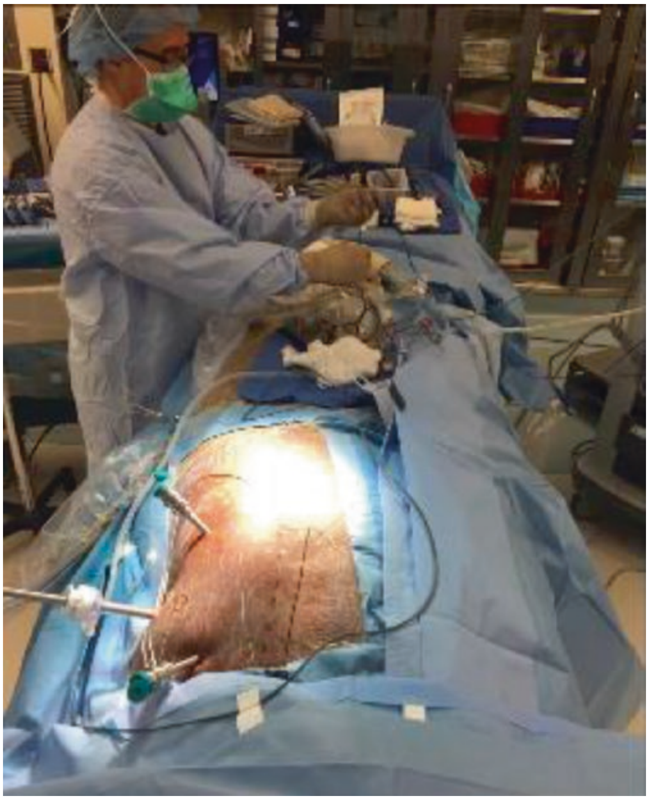


Fig. 20.1 Final patient positioning with the robotic ports in the left chest

After docking of the robot, the first step is to open the pericardium to visualize the LAD. An initial pericardial incision is made posterior to the left phrenic nerve, which will serve as a drainage channel for blood to leave the pericardium. Next, the fat is stripped off the anterior pericardium and the second pericardiotomy is performed; the LAD is visualized and the final determination is made regarding the feasibility of robotic MIDCAB grafting. Thereafter, LITA harvest begins with opening of the endothoracic fascia along the length of the vessel with robotic cautery shears. Once partially exposed, the LITA is taken down using bipolar graspers and a monopolar spatula tool in a skeletonized fashion. LITA braches are clipped and incised (Fig. 20.2). Once the entire length is freed, the most distal end is closed using a large plastic clip that has a suture tied to it (Fig. 20.3). The suture attached to the clip is fastened to the opened medial pericardial edge with a small metallic clip so that the LITA can be found once the anterior mini-thoracotomy is made.

A site for anastomosis is picked and the anterior mini-thoracotomy is made. A soft tissue retractor is placed followed by a self-retaining retractor. The LITA is then inspected and a combination of milrinone, heparin, and blood is injected into the LITA to promote vasodilation. Heparin is dosed to achieve an ACT >350 s. An off-pump stabilizing device is placed through the caudal most port site and the site of anastomosis is stabilized. A vessel loop is placed around the LAD, proximal to the anastomosis site and the LAD arteriotomy is made. An intracoronary shunt may be inserted as dictated by coronary anatomy and myocardial ischemia. The anastomosis is completed in the usual fashion by manual suturing under direct vision. A transit time flow probe is routinely used to check the anastomosis and graft quality. Hemostasis is carefully ensured and 19 French soft drains are placed in both the caudal two port sites. Once in the intensive care unit, the patient is given aspirin and clopidogrel within 6 hours of surgery, after it is ascertained that the patient is not bleeding.

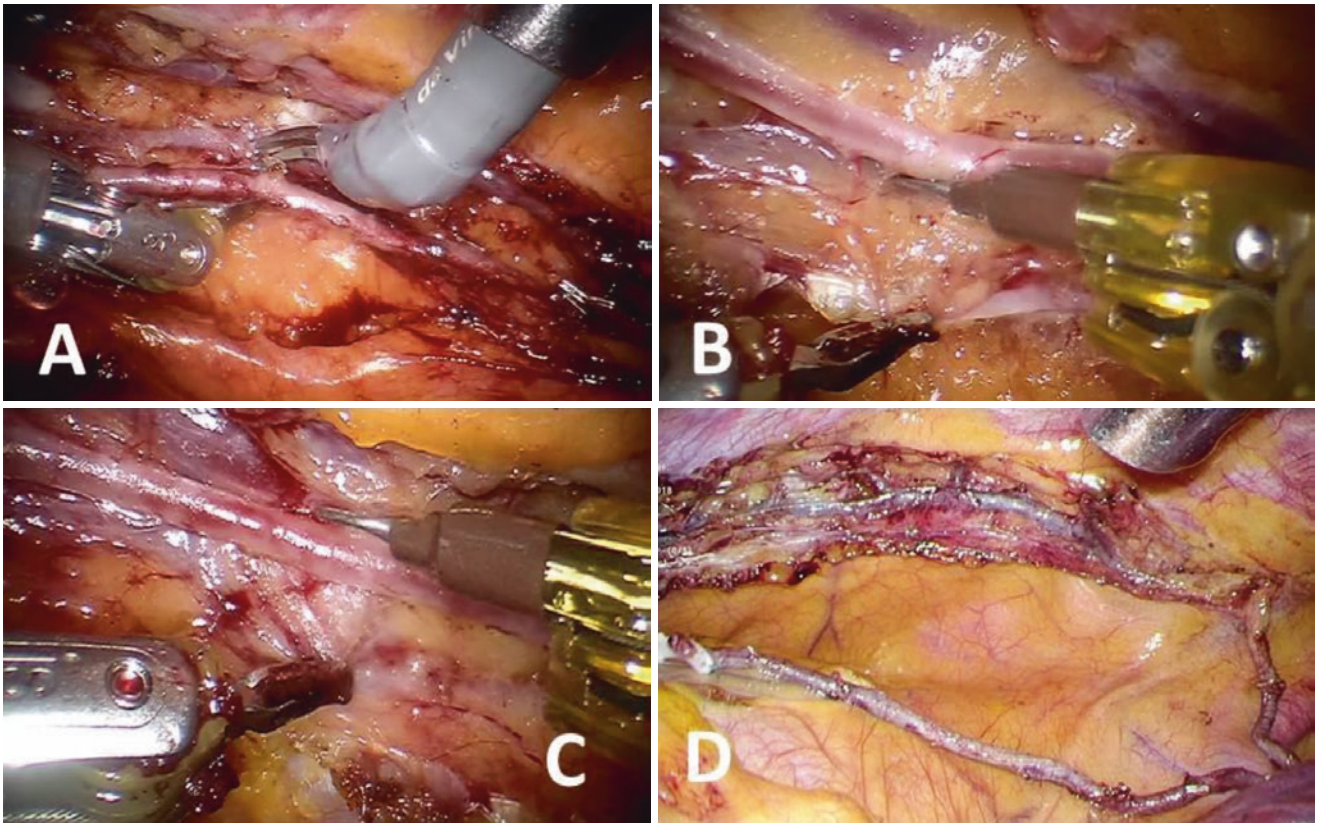
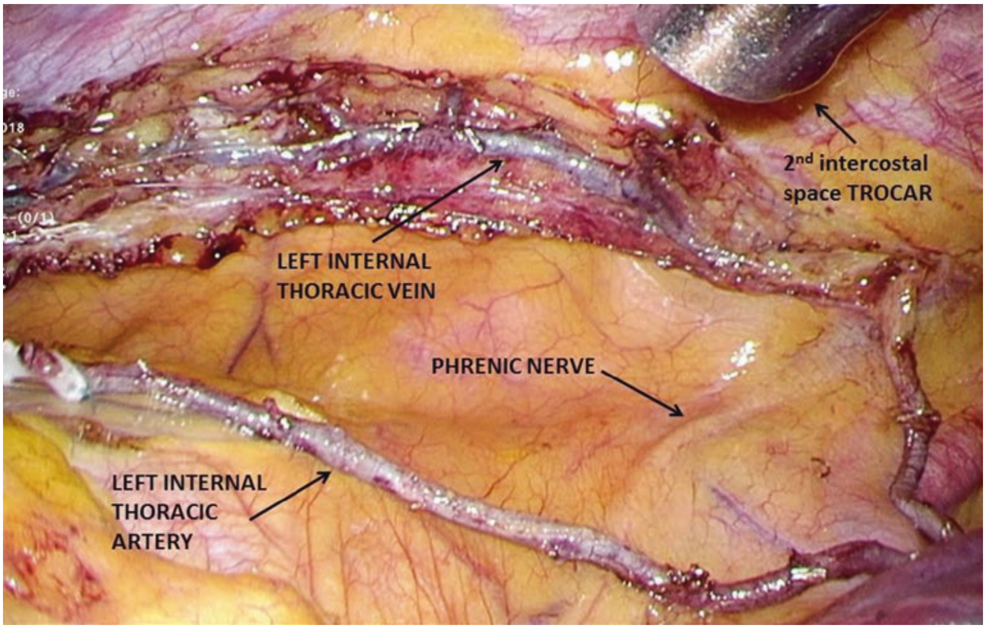


Fig. 20.2 Robotic takedown of the left internal thoracic artery (LITA). (**a**) Branches of the LITA are cut after clips are applied. (**b**, **c**) The spatula and bipolar graspers are utilized to carry out blunt skeletonization of the LITA. (**d**) The LITA is distally clipped and separated from the chest wall

Fig. 20.3 The left internal thoracic artery has been completely robotically skeletonized and separated from the chest wall


2nd intercostal space TROCAR
LEFT INTERNAL THORACIC VEIN
PHRENIC NERVE
LEFT INTERNAL THORACIC ARTERY

Timing of Interventions

HCR can be sequenced in one of three ways: concomitantly in a hybrid OR, staged with CABG before PCI, or staged with PCI then CABG. Each has its own advantages and disadvantages.

Concomitant HCR requires a hybrid operating room where CABG and PCI can be performed. Typically, the CABG is performed first with PCI to follow immediately after. This allows for direct angiographic assessment of the LITA-to-LAD anastomosis during the PCI procedure. Additionally, there may be a higher degree of patient satisfaction given that all interventions are completed in a single setting. However, there does exist a concern for postoperative bleeding due to the need for immediate dual antiplatelet therapy. Also, special care should be taken in patients with kidney disease as they receive a dual nephrotoxic insult of surgery followed by intravenous contrast administration.

Staged CABG followed by PCI allows for angiographic evaluation of the LITA-to-LAD anastomosis as well as PCI in the setting of a protected anterior wall (Fig. 20.4). This provides some degree of protection for PCI of the non-LAD vessels. Furthermore, the risk of bleeding is lower and allows for full dual antiplatelet therapy with minimal perioperative bleeding risk. However, there is a small risk of ischemia during the CABG procedure as the diseased non-LAD vessels are unaddressed at the time of surgery. Furthermore, in the setting of an unsuccessful PCI, the patient may require surgical reintervention.

Staged PCI followed by CABG is clearly useful in the setting of myocardial infarction when the culprit lesion is not the LAD. Also, the risk of ischemia during CABG is lower and the in situ LITA can be assessed by angiography before surgery. Several drawbacks of a PCI first approach are that there is no angiographic assessment of the LITA-to-LAD graft, an increased risk of bleeding due to pre-CABG use of dual antiplatelet therapy, as well as a potentially increased risk of stent thrombosis during surgery secondary to the inflammatory response to surgery as well as the discontinuation of antiplatelet therapy.

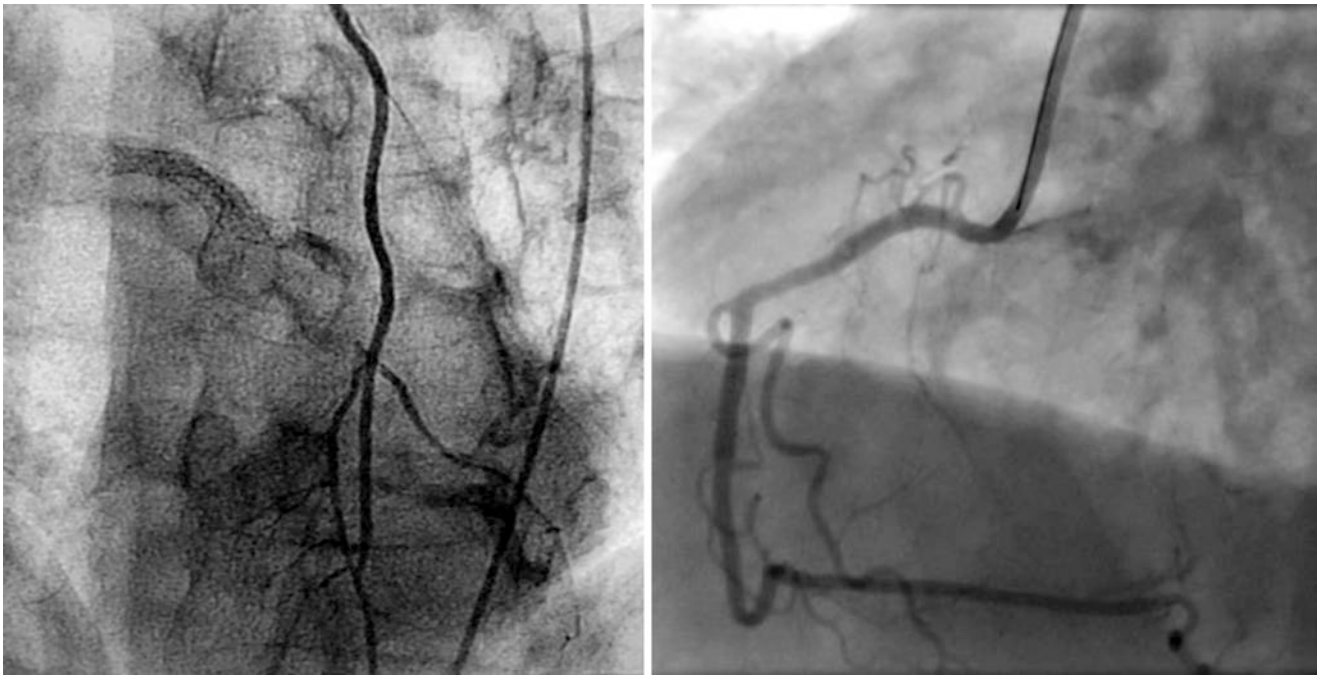


Fig. 20.4 Results of a staged robotic-assisted MIDCAB followed by PCI of the mid RCA. When CABG is done first, the LITA-to-LAD anastomosis can be assessed during PCI. *CABG* coronary artery bypass grafting, *LAD* left anterior descending, *LITA* left internal thoracic artery, *PCI* percutaneous coronary intervention, *RCA* right coronary artery

Results

The majority of data concerning HCR comes from multiple single centers' experience, totaling over 3000 patients receiving HCR. By far, CABG first HCR was the most popular (50.6%), followed by PCI first HCR (26.6%). Perioperative mortality ranged from 0–2.6% among the series and most series reported reduced morbidity compared to conventional CABG (decreased transfusion requirements, shorter intensive care unit and hospital length of stays, as well as faster recovery). Survival rates from these HCR registries are 92.5–100% at 1 year and 84.8–93% at 5 years [15].

The POL-MIDES (Prospective Randomized Pilot Study Evaluating the Safety and Efficacy of Hybrid Revascularization in Multivessel Coronary Artery Disease) consisted of 200 consecutive patients with multivessel CAD involving the proximal LAD and at least one other non-LAD vessel amenable to both PCI or CABG. These patients were randomized in a 1:1 fashion to MIDCAB and PCI or conventional CABG. At 1 year, all-cause mortality was similar and non-statistically significant: 2.9% for CABG and 2% for HCR. So too was freedom from major adverse cardiac events: 92.2% for CABG and 89.8% for HCR [16].

The Hybrid Observational Study was the first multicenter prospective cohort study for patients undergoing HCR. In this study, 200 patients underwent HCR and were compared to 98 patients who, though HCR eligible, underwent PCI. No difference in cerebrovascular or major adverse cardiac events was seen at 1 year. However, the two groups diverged at 18 months, favoring HCR [17].

In 2017 the National Institutes of Health funded a prospective randomized trial comparing HCR versus PCI. Funding was halted by the NIH in 2019 due to slow enrollment. Long-term follow-up of 200 patients enrolled in this trial may shed some light on future decision-making regarding the care of multi-vessel CAD patients.

Conclusions

HCR is a viable option for carefully selected patients with multivessel CAD, combining the best features of both CABG and PCI. With the ever-aging population, less invasive options that limit patients' exposure to periprocedural morbidity are growing in favor. Additionally, HCR offers patients who would otherwise be treated with multivessel PCI rather than conventional CABG surgery an opportunity to receive the long-term benefit of a LITA-to-LAD graft. Furthermore, HCR serves to bridge the gap between cardiologists and cardiac surgeons, encouraging collaboration rather than competition. Further investigation into this modality of CAD treatment is promising and necessary.

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21

Bilateral Internal Mammary Artery Grafting

Shahzad G. Raja and David Taggart

High Yield Facts

- Left internal mammary artery (IMA) grafting of left anterior descending artery is the "gold standard" of revascularization.
- Overwhelming evidence from observational studies suggests that bilateral IMA grafting is associated with better long-term outcomes including improved survival, enhanced freedom from re-intervention and better symptom relief.
- Bilateral IMA grafting provides incremental beneficial effect with time.
- Bilateral IMAs can be used in various configurations.
- Diabetics are less frequently offered BIMA grafting due to concerns about sternal wound complications.
- Skeletonization technique for IMA harvesting lowers the risk of sternal wound complications in all patients and particularly in those with diabetes.
- Arterial Revascularization Trial (ART) is the only randomized trial of bilateral IMA versus single IMA with a primary outcome of survival at 10 years.
- The 5-year interim analysis of ART reports similar survival and increased sternal wound infection.

Introduction

Coronary artery bypass grafting (CABG) remains one of the most commonly performed cardiac surgical operations for over half a century and there are currently approximately three-quarters of a million such operations performed worldwide annually [1]. The success of CABG is attributed to improved survival, reduction in myocardial infarction and repeat revascularization compared to percutaneous coronary intervention [2, 3]. There is increasing evidence to suggest that the choice of conduits for CABG is central to the long-term success of CABG. Conventionally, most patients undergoing CABG receive the standard operation comprising of a single internal mammary artery (IMA) with additional vein grafts performed using cardiopulmonary bypass. However, the last couple of decades have confirmed superiority of arterial grafts compared to vein grafts [4, 5]. Amongst the arterial grafts, bilateral IMAs have been the most extensively investigated and reported conduits.

The use of bilateral IMAs during CABG has been established as a determinant of improved long-term survival and event-free cardiac survival [6]. Cardiac benefits are sustained throughout the first 20 postoperative years, and bilateral IMA grafting is now being increasingly recommended in patients with a life expectancy of 10 years or longer at the time of CABG [6, 7]. Despite these well-recognised advantages of bilateral IMA grafting, the prevalence of bilateral IMA use in contemporary practice remains significantly low, comprising 4% and 10% of CABG operations in the United States and Europe, respectively [8]. Possible explanations for these extremely low adoption rates include a perceived high risk of sternal complications and concerns related to the technical complexities of the strategy.

This chapter provides an overview of bilateral IMA grafting focusing on the rationale, surgical aspects, outcomes, and concerns associated with this strategy.

Historical Aspects

The initial enthusiasm for the utilization of the left IMA as a bypass graft was prompted by the encouraging results of the work by Arthur Vineberg in 1946 [9]. Subsequently, Vasilii Kolesov, a Russian cardiac surgeon, performed the first sutured anastomoses of left IMA to the left anterior

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descending (LAD) artery in 1964 [10]. Reports about the application of bilateral IMAs for myocardial revascularization can be traced back to the sixties, when Rene Favalaro, considered the 'father' of coronary surgery, described the technique and outcomes of bilateral IMA implants into the myocardium [11]. However, the discovery of saphenous vein as a conduit for CABG, around the same time, made it the most commonly utilized graft during the seventies, eighties [12] and even today due to the ease of harvest, better handling properties, excellent procedure reproducibility and favorable immediate outcomes [13]. The publication of the landmark paper from the Cleveland Clinic group reporting improved 10-year survival and freedom from recurrent angina, myocardial infarction and the need for repeat revascularization for the left IMA to LAD graft substantiated the status of this grafting strategy as standard practice [14].

Suzuki and associates were the first to report the use of bilateral IMA grafts to revascularize the coronary arteries by conventional direct anastomoses in 1973 [14]. This was followed by the publication of excellent clinical outcomes of bilateral IMA grafting by the Cleveland Clinic group in 1983 [15]. However, regular use of bilateral IMAs for coronary revascularization was adopted initially only by few centers [16–20] and despite superior results achieved with bilateral IMA grafting [15, 21], the adoption rates are disappointingly low worldwide. Currently approximately 20% of CABG in Europe and less than 5% in the USA are performed using bilateral IMAs [22].

Rationale

The excellent patency rates of bilateral IMAs, resulting in superlative long-term performance manifested as better relief of symptoms, low reoperation rate and superior long-term survival compared with saphenous vein grafts [15], is the predominant reason for propagation of the concept of bilateral IMA grafting. Central to the outstanding performance of bilateral IMAs are their unique histological features, better physiological characteristics and protective genomics [23] (Table 21.1).

Table 21.1 Characteristics of internal mammary arteries

Anatomical features	Physiological features	Genomics
• Mean luminal diameter of 1.5 ± 0.36 mm • Fewer muscular fibers and greater number of elastic lamellae in the media • Medial thickness of 0.10–0.60 mm • Non-fenestrated internal elastic lamina	• Larger quantities of vasodilators such as nitric oxide and prostacyclin generated by endothelium • Endothelium-dependent relaxation factor mediated protection against vasoconstrictors • Protection against progression of atherosclerosis distal to anastomoses due to downstream flow of endogenous vasodilators	• Down-regulation of genes in the annotated atherosclerosis signaling pathway • Down-regulation of genes for signaling pathway for eicosanoids

The IMAs are resistant to atherosclerosis [24] and intimal hyperplasia [25] due to their favourable anatomical and physiological features. Additionally, the IMA also has the ability to remodel itself after its use as a bypass graft, due to endothelium-related mechanisms, resulting in an increase in diameter and concomitantly increased flows over time after CABG [26].

The radial artery and the saphenous vein are still more commonly used as second choice conduits after the left IMA, despite seemingly compelling evidence of superior outcomes with the bilateral IMAs [23]. The early development of atherosclerosis in vein grafts compromising their long-term patency rates so much so that almost 50% of the vein grafts are occluded by the end of the first decade is a phenomenon that was described over 30 years ago [27] and remains the Achilles heel of saphenous vein grafts even today. After the revival of the radial artery as a conduit in 1993, several studies have been published to determine its performance in comparison to the right IMA [23]. Most reports have provided strong evidence for the superiority of the right IMA compared to the radial artery as a second choice conduit after the left IMA [28–30]. However, there are still some studies like the one published recently by Tranbaugh et al. that fuel the controversy about the second best arterial graft [31].

Technical Aspects

Several surgical strategies have been used to achieve left-sided myocardial revascularisation with bilateral IMAs grafting [32]. These include retrosternal in-situ right IMA to the LAD and the left IMA to circumflex marginal branches, directing the right IMA through the transverse sinus in a retroaortic course, and free right IMA graft connected proximally either to the left IMA (composite grafting) or to the ascending aorta (Fig. 21.1). Each one of these surgical strategies for bilateral IMA grafting has its merits and demerits (Table 21.2).

Retroaortic In-Situ Right IMA Via Transverse Sinus to Circumflex Marginal Branches with In-Situ Left IMA to LAD

In 1984, Puig et al. [33] were the first to report the use of retroaortic in-situ right IMA via the transverse sinus for circumflex artery grafting. The surgical technique for in-situ pedicled right IMA harvest is similar to the one used to take

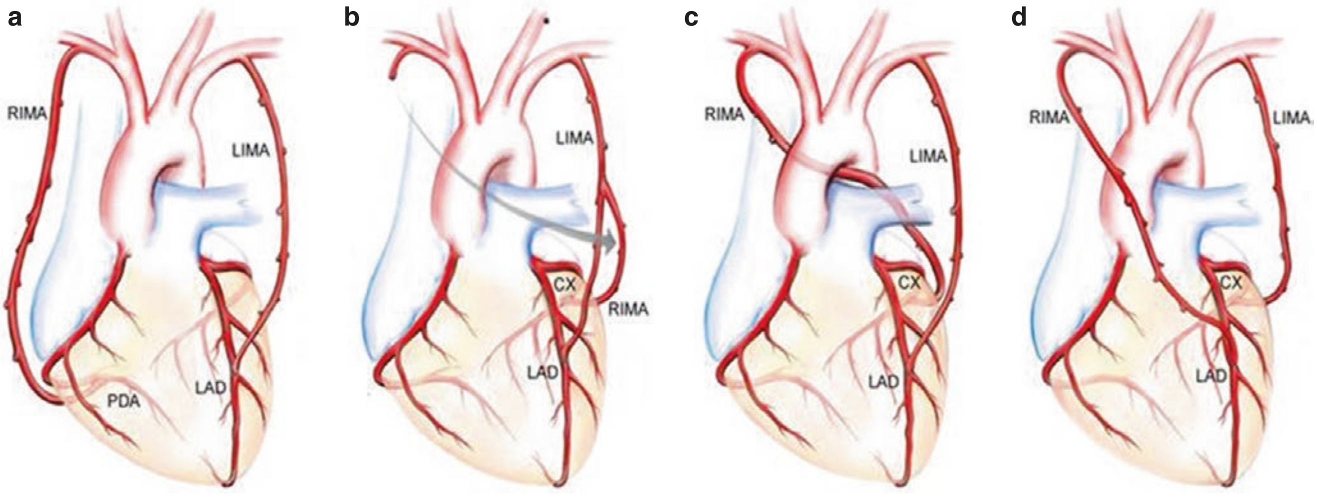

Fig. 21.1 Various configurations of bilateral IMAs. (**a**) In-situ RIMA to the PDA and in-situ LIMA to the LAD. (**b**) LIMA-RIMA Y graft with in-situ LIMA to the LAD and RIMA to the Cx branches. (**c**) In-situ RIMA through the transverse sinus to the Cx branches and in-situ LIMA to the LAD. (**d**) Retrosternal in-situ RIMA to the LAD and in-situ LIMA to the Cx branches. *Cx* circumflex artery, *IMAs* internal mammary arteries, *LAD* left anterior descending artery, *LIMA* left internal mammary artery, *RIMA* right internal mammary artery, *PDA* posterior descending artery. (Illustration by Marcie Bunalade)

Table 21.2 Pros and cons of various surgical strategies for BIMA grafting

Aspect	Retro-aortic in-situ RIMA	Retrosternal in-situ RIMA	Composite T or Y grafting	RIMA to RCA
Pros	• LAD is revascularised by the gold standard in-situ LIMA • Left coronary system is perfused by two in-situ IMAs • Avoids the difficulties of anastomosing a thin-walled free RIMA to a thick-walled aorta • No grafts crossing the midline behind the sternum • Possibility to easily apply the no-touch principle by using different composite graft configurations	• Easily reproducible • Technically less demanding • LAD is grafted by an intact in-situ IMA • Complete left-sided IMA grafting is readily achieved • Principle of multiple-origin blood supply is maintained	• Aortic “no touch” technique reduces the risk of stroke • Greater length of RIMA is available for more extensive myocardial revascularisation (avoiding the use of a third conduit)	• Easy to anastomose in-situ RIMA to main RCA
Cons	• Inability to control bleeding from retroaortic RIMA branches • Aortic compression of the in-situ RIMA • Compromised graft patency because of undetected kinks, graft overstretching, rotation, and spasm of distal RIMA	• Potential risk of damage to the artery during repeat sternotomy	• Single source blood supply • Potential steal phenomenon • Competitive flow • Hypoperfusion syndrome	• Inferior patency rate to that of the in-situ LIMA to LAD

BIMA bilateral internal mammary arteries, *LAD* left anterior descending artery, *LIMA* left internal mammary artery, *RCA* right coronary artery, *RIMA* right internal mammary artery

down the left IMA. The right IMA is mobilised with its adjacent veins, the surrounding fat or muscular tissues, and the endothoracic fascia. This pedicle is about 2 cm wide. The right IMA is extensively dissected from its distal bifurcation in the rectus muscle up to the level of the subclavian vein. The RIMA at its subclavian origin is freed from its pleural and thymic attachments and if necessary the confluence between the RIMA vein and the azygos vein is divided to gain a maximum [34]. Care is taken during this dissection not to injure the phrenic nerve. After dissection the right IMA is forcefully sprayed with a solution of papaverine (40 mg/100 ml) and wrapped with gauze soaked in the same solution. The RIMA is divided after cannulation for on-pump CABG or prior to exposing the target vessels in off-pump CABG. The right IMA flow is usually assessed by checking the force of free bleeding [32].

Next the pericardium anterior to the superior vena cava is cut down transversely and the right IMA is passed behind the ascending aorta and the pulmonary artery through the transverse sinus. The pleural strip that covers the ventral side of the pedicle is used as a guide to avoid any twisting of the right IMA. The pedicle is considered adequately positioned in the transverse sinus only when the free bleeding from the right IMA remains brisk. The left ventricle is then lifted and rotated to the right to expose its lateral wall. Anastomosing the right IMA to the circumflex marginal branches in this position is easier than when the heart is not rotated but, on the other hand, requires additional length of the right IMA. The pedicle may sometimes be tight during this part of the operation. However, the release of the heart after completion of the anastomoses always restores adequate length and laxity to the right IMA. The in-situ left IMA is anastomosed to the LAD in the conventional fashion [32].

Retrosternal Crossover In-Situ Right IMA to LAD with In-Situ Left IMA to Circumflex Marginal Branches

The in-situ right IMA is harvested as a pedicled or skeletonised conduit. Following assessment of flow and length the right IMA is directed anterior to the aorta to graft the LAD. Preventive measures are taken with respect to repeat sternotomy. The RIMA is tunnelled through a right pericardial incision at the level of the aorta and pulmonary trunk and directed leftward, crossing the midline at the most cranial point before angling toward the LAD. This manoeuvre allows free space on the aorta for future instrumentation and provides a safety distance between the IMA and the sternum. An in-situ left IMA Is used to graft the circumflex branches [32].

A giant metal clip is used to mark the right IMA midline location with respect to the sternum for a possible future median sternotomy [35]. Mediastinal fat is used to cover the artery and fix it in the selected route to prevent tenting after removal of the retractor and closure of the sternum.

The retrosternal crossover in-situ right IMA to LAD arrangement is best avoided when the distal IMA bifurcation cannot loosely reach the LAD. In this category are patients with a short right IMA, a very long ascending aorta, an enlarged right ventricle, or an LAD anastomotic site that is too distal or unpredictable [35].

Composite Left IMA-Right IMA T or Y Grafting

Sauvage et al. [20] were the first to propose the T or Y graft configuration constructed by the left IMA anastomosed to the LAD and by a free right IMA anastomosed to the left IMA proximally in an end-to-side fashion and connected distally to a marginal branch of the circumflex artery. Both IMAs are harvested as pedicled, skeletonised or semi-skeletonised conduits. After heparinization, the right IMA is harvested as a free graft. The left IMA is also divided at its distal bifurcation. Following selection of the target site for right IMA there are two possible approaches for constructing the T or Y graft.

The first strategy involves anastomosis of the distal end of the right IMA in an end-to-side manner in parallel to its target vessel. If only bilateral IMA are being used for complete myocardial revascularisation, the right IMA is then anastomosed sequentially with side-to-side perpendicular anastomoses to the left ventricular free wall vessels. It is then anastomosed proximally in an end-to-side manner in parallel to the left IMA. The left IMA is then anastomosed in parallel to the anterior wall vessels [32].

The second strategy involves the construction of the proximal anastomosis of the right IMA with left IMA first. The proximal anastomosis is constructed at the level of the pulmonary annulus. The bilateral IMA Y or T graft as a result is composed of the left IMA being the short limb of the Y graft, and the left IMA the long one. Depending on the length of the right IMA it is then possible to graft as far as the lateral circumflex or posterior descending arteries [32].

Right Internal Mammary Artery for Grafting the Right Coronary System

Although bilateral IMAs are being increasingly used for left-sided coronary system it is not unusual to use the pedicled or skeletonised right IMA either as in-situ or free graft to the right coronary system with the left IMA anastomosed to the LAD [36]. The technique of harvest of right IMA and anastomosis to the right coronary system is similar to that for the left coronary system. Generally, when the right coronary system is grafted, the posterior descending artery is the preferred site, the important determinant being avoidance of atheroma at the site of anastomosis or more distally. If the required length of the in-situ right IMA is short then it is best used as a free graft. In case of free right IMA several options are available for proximal anastomosis. The proximal anastomosis can be constructed directly on to the ascending aorta. If the aorta is thick or atheromatous or if the length is not adequate to reach the aorta, then the proximal anastomosis can be constructed directly onto a saphenous vein graft, radial artery or onto the proximal left IMA as a Y or T graft depending on which supplemental conduits have been used. Occasionally a vein patch on the aorta can be used to facilitate the anastomosis [32].

Clinical Outcomes

The evidence base for the use of bilateral IMAs is predominantly in the form of several observational studies comparing the results of single IMA with bilateral IMAs [37–40].

Interestingly, to date despite the significance of the issue of bilateral IMA usage, only one randomized controlled trial (RCT), the Arterial Revascularisation Trial (ART) [41], has been conducted. The long-term results of ART are awaited and therefore there continues to be no definitive evidence in the form of a RCT with regard to the long-term benefits of bilateral IMA grafting, which has been a major barrier against the use of BIMA.

Evidence from Observational Studies

The Cleveland Clinic Group was the first to report long-term benefits of bilateral IMA grafting as early as 1983 [15]. They reported that bilateral IMA grafting yielded excellent graft patency, relief of symptoms (69% asymptomatic and 28% mild angina), low reoperation rate (1%) and long-term survival (97.2% at 7 years and 90.2% at 9 years after CABG) [15]. Similar outcomes were reported by other groups for bilateral IMA grafting in the mid to late 1980s [16–20]. With further follow-up, it became evident that survival improved with bilateral IMA usage [42]. Another pioneering publication from the Cleveland Clinic Group in the late 1990s further strengthened the evidence in support of bilateral IMA use [43]. It involved an analysis of two groups (single IMA vs bilateral IMAs), each containing more than 1000 patients, who were followed up for more than 10 years. Patients undergoing single IMA grafting had significantly higher rate of death, reoperation and percutaneous intervention than those who received bilateral IMAs. Several other studies supported these findings [37, 38] including a meta-analysis of 15,962 patients undergoing 11,269 single IMA and 4693 bilateral IMA grafts that reported a significantly better survival for patients who received bilateral IMA grafts (HR 0.81; 95% CI:0.7–0.9) [21].

The Cleveland Clinic Group published their third landmark paper comparing single IMA with bilateral IMAs in 2004 [6]. It included 1152 propensity-matched pairs of patients receiving single or bilateral IMAs with additional grafts as required. The mean follow-up was 16.5 years. This study was the first to show that the survival benefit of BIMA grafting extended beyond the second decade after surgery. Furthermore, single IMA grafting was found to be a risk factor for death in the constant and late phase of follow-up. An analysis of subsets, such as patients with left ventricular dysfunction, non-cardiac morbidities, etc. also revealed that these subgroups benefitted significantly from bilateral IMA grafting [6]. Kurlansky et al. [44] substantiated these findings by publishing a large propensity-matched study with 30-year follow-up. It revealed that in relation to survival, bilateral IMA grafting favoured women, elderly patients, diabetics, and patients with left ventricular and preoperative renal dysfunction [45]. A recently published meta-analysis of 27 observational studies that included 79,063 patients (19,277 bilateral IMA; 59,786 left IMA) also demonstrated significantly better long-term survival for bilateral IMA recipients (HR 0.78; 95% CI:0.7–0.8; $p < 0.00001$) [44].

Apart from survival benefit, bilateral IMA grafting is also associated with a reduction in myocardial infarction and repeat revascularization [40, 46]. Rankin et al. [46] reported that the average event-free survival over 20-years was extended by almost 1 year with the use of bilateral IMAs [46]. Stevens and associates also found bilateral IMA grafting to be associated with a reduced risk of death, myocardial infarction, and coronary reoperation throughout the mean follow-up period of 11 ± 3 years [40].

Evidence from Arterial Revascularization Trial

The Arterial Revascularisation Trial (ART) is a randomized trial of bilateral IMAs vs single IMA, with a primary outcome of survival at 10 years [41] (Table 21.3). The trial enrolled CABG patients in 28 hospitals in seven countries. Three thousand one hundred and two patients were randomly assigned to single IMA ($n = 1554$) or bilateral IMAs ($n = 1548$). The mean number of grafts was 3 for both groups. Forty per cent of the single IMA procedures and 42% of the bilateral IMAs were performed off-pump. Mortality at 30 days was 18 of 1548 (1.2%) for single IMA and 19 of 1537 (1.2%) for bilateral IMAs, and at 1 year was 36 of 1540 (2.3%) and 38 of 1529 (2.5%), respectively [53]. The rates of stroke, myocardial infarction, and repeat revascularization were all ≤2% at 1 year and similar between the two groups [53]. Sternal wound reconstruction was required in 0.6% and 1.9% of the single IMA and bilateral IMA groups, respectively.

The recently published interim 5-year analysis of ART showed that the rate of death was 8.7% in the bilateral IMA group and 8.4% in the single IMA group (hazard ratio, 1.04; 95% confidence interval [CI], 0.81–1.32; $p = 0.77$), and the rate of the composite of death from any cause, myocardial infarction, or stroke was 12.2% and 12.7%, respectively (hazard ratio, 0.96; 95% CI, 0.79–1.17; $p = 0.69$). The rate of sternal wound complication was 3.5% in the bilateral IMA group versus 1.9% in the single IMA group ($p = 0.005$), and the rate of sternal reconstruction was 1.9% versus 0.6% ($p = 0.002$) [54].

Publication of these 5-year interim results once again raised questions about the benefits of bilateral IMA grafting as well as various technical aspects of ART [55]. It is important to emphasize that the ART was planned as a “real world” pragmatic trial to understand the feasibility, efficacy, and safety of bilateral IMA grafting. Furthermore, it is vital to highlight that any potential benefits of bilateral IMA grafting might show up only over a minimum of 10 years, and owing to improvements in care, this follow-up period may need to be even longer [55].

Table 21.3 Impact of skeletonization on incidence of sternal wound infection

Author	Patient group	Study type (level of evidence)	Outcome(s)	Key result
Peterson et al. [47]	79 diabetics who received skeletonized and 36 diabetics who received pedicled IMA	Retrospective level 3	Prevalence of sternal wound infection	Significantly lower incidence of deep sternal wound infection (1.3% vs 11.3%; $p = 0.03$) as well as overall sternal infection (5.1% vs 22.2%; $p = 0.03$) in patients with skeletonized IMA
Pevni et al. [48][a]	1000 consecutive patients who received skeletonized BIMA	Retrospective level 3	Risk of deep sternal wound infection	Deep sternal wound infection rate was 2.2% with no difference in the rate of deep sternal wound infection among the specific high-risk groups (i.e., diabetic, obesity, female, and elderly) compared with patients without these risk factors
Matsa et al. [49][a]	231 diabetic and 534 nondiabetic patients with skeletonized BIMA	Retrospective level 3	Early and midterm outcomes	Comparable incidence of deep sternal wound infection in diabetics and nondiabetics (2.6% vs 1.7%; $p = 0.40$)
Kramer et al. [50][a]	303 consecutive patients ≥70 years with skeletonized BIMA	Retrospective level 3	Early and midterm outcomes	Only 6 patients (2%) had deep sternal wound infection
Sofer et al. [51][a]	545 consecutive patients with skeletonized BIMA	Retrospective level 3	30-day and 1-year outcomes	9 patients (1.7%) had deep infections and 15 (2.8%) had superficial infections
Bical et al. [52]	560 consecutive patients with skeletonized BIMA, including 63 diabetics	Retrospective level 3	Early and 7-year follow-up outcomes (mean, 29 ± 20 months)	6 patients (1.1%) had sternal complications. No wound complications were observed in diabetic patients

IMA internal mammary artery, *BIMA* bilateral internal mammary arteries
[a]Metachronous studies from the same center

Concerns

Increased risk of deep sternal wound infection (DSWI), particularly in patients with diabetes, obesity and chronic obstructive pulmonary disease, is cited as the key concern for bilateral IMA use [56]. In addition, the technical complexity of the harvesting technique, the longer operative time associated with it and potential increase in short-term morbidities are also seen as obstacles that prevent widespread uptake of bilateral IMA grafting [57]. A recently published meta-analysis [58] confirmed the strong association, of bilateral IMA harvesting with an increased incidence of DSWI, which is in line with previous reports, in particular, the ongoing ART, which also found the rates of sternal wound complications at 5 years [54] and sternal wound reconstruction at 1 and 5 years [53, 54] to be increased after bilateral IMA grafting. The well-known reason for this is an acute postoperative de-vascularisation of sternum, which is exacerbated after bilateral IMA harvesting, and thereby increasing the risk of DSWI [59]. Deep infection increases the risk of sternal necrosis with greater need for sternal resection [58]. Although the occurrence of DSWI is relatively low [58], DSWI serves as a continuing detrimental risk factor for long-term survival [60]. It should be stressed that even though patients with diabetes are more prone to sternal infection and its poorer healing, they may actually have the most to gain from bilateral IMA grafting as they often present with severe and diffuse coronary artery disease [56, 61].

Skeletonization of IMA (a technique pioneered by Sauvage and colleagues [20]) has been advocated to decrease the occurrence of sternal wound infections [47–52] (Table 21.3) and increase the number of arterial anastomoses [62]. Skeletonization involves meticulous dissection of the IMA conduit away from the chest wall with preservation of the collateral sternal blood supply and the internal thoracic veins. On the other hand, when skeletonized, the vessel loses its “milieu,” which theoretically may adversely affect its long-term resistance to arteriosclerosis. This coupled with the lack of long-term patency studies of the skeletonized IMA and meticulous follow-up and confirmation by angiography raises concerns about whether this technique sacrifices the superior longevity of the conduit [62].

Conclusion

The LIMA to LAD graft is considered the “gold standard” of CABG. This conduit use is associated with improved survival, better symptomatic relief, increased freedom from myocardial infarction, and enhanced freedom from re-intervention when compared to saphenous vein grafting. It has proven superior long term patency with clinical and angiographic outcomes that are unmatched by other conduits. Given the fact that patients with multivessel coronary artery disease often require more than one graft during CABG, the notion of “two IMAs are better than one” makes bilateral IMA grafting an attractive revascularization strategy. Bilateral IMA grafting has been extensively studied with multiple retrospective and prospective cohort studies validating the safety and efficacy of this approach. However, concerns regarding perioperative complications, particularly DSWI, and the technical challenges involved in utilizing and teaching the technique have limited its widespread use. It is expected that long-term follow-up of ART and its sub analyses will allay the anxieties and address the concerns associated with bilateral IMA grafting.

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Total and Multiple Arterial Revascularization

22

James Tatoulis

High Yield Facts

- Arterial graft patency rates are always better than those of saphenous vein grafts (90–95% vs 50–60% at 10 years).
- Perioperative results for both total arterial revascularization (TAR) and multiple arterial bypass grafting (MABG) and single arterial (conventional) coronary artery bypass grafting (CABG) are excellent and identical (1% perioperative and 30 day mortality).
- For every 100 patients having CABG, 10 more will be alive at 10 years postoperatively (80–88% versus 70–78%) if they had multiple arterial grafts.
- In TAR/MABG, multiple graft strategies and combinations can be used and are equally effective as well as on- or off-pump.
- The second arterial graft should be to the next most important vessel (amount of ischemic myocardium subtended).
- Arterial graft patency rates are similar, irrespective of which arterial conduit, if it is anastomosed to the same target vessel, with the same degree of native coronary artery stenosis.
- In general, patency rates to the left anterior descending (LAD) at 10 years are 90–95%, circumflex artery 90%, and posterior descending artery 80–90%.
- TAR/MABG enhances prognosis in older patients, women, diabetics, and those with preoperative renal dysfunction.
- Spasm prophylaxis and avoidance of competitive flow are essential for all arterial grafts—especially radial artery and right gastroepiploic artery.

Introduction and Rationale for Arterial Coronary Grafting

Conceptually, coronary artery bypass graft surgery (CABG) has not changed since 1967 when aortocoronary saphenous vein grafts (SVGs) were used to bypass stenotic coronary lesions [1]. Symptomatic relief and enhanced prognosis especially in triple vessel disease, left main, and proximal severe left anterior descending (LAD) stenosis, remain the goals of CABG.

The success of the left internal thoracic artery (LITA) to the LAD transformed CABG—now the single most important strategy in coronary surgery since 1986 [2]. LITA to the LAD and SVGs to all other vessels has subsequently been the standard of practice. Currently, over 70% of all coronary grafts are SVGs [3]. Unfortunately, SVGs fail—10% at 1 week, 25% at 1 year, and 50% at 10 years from technical problems (early), intimal and media hyperplasia (midterm), and atheroma (long-term) [4, 5] (Fig. 22.1). Disappointed with the development of occlusive atheroma in SVG, poor long-term SVG patency and results, cardiac surgeons have explored multiple arterial bypass grafting (MABG), and total arterial revascularization (TAR) (Fig. 22.2).

If one ITA was better than none, additional/MABG should provide incrementally better long-term outcomes, with a goal of TAR as the optimum, when appropriate and achievable. Arterial coronary grafts remain free of atheroma and have better patency rates—90–95% at 10 years—[2, 5, 6], resulting in less recurrent angina, fewer myocardial infarctions (MI) and reoperations and better survival than with SVGs. Hence it is logical to use arterial grafts instead of SVGs [7]. Multiple large studies have documented better long-term outcomes for CABG with two ITAs over one [8]. Arterial grafts (unlike SVGs) also synthesize and release nitric oxide and other favourable vasoactive agents that protect the coronary artery downstream from development of further atheroma [9].

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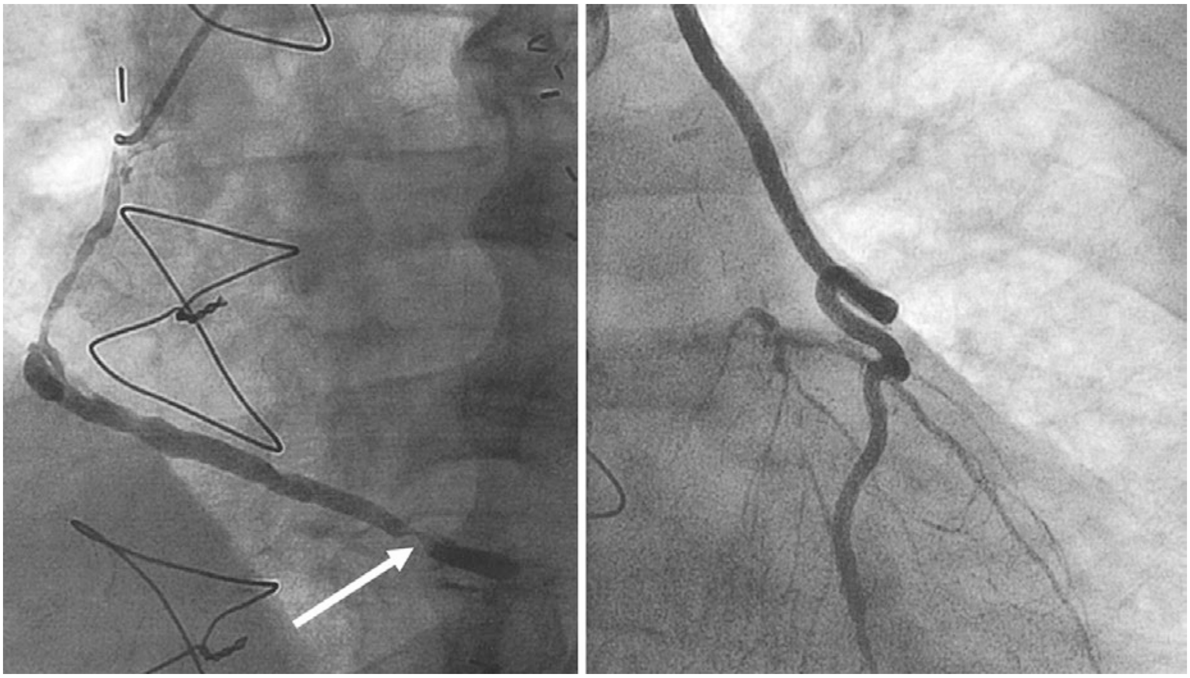

Fig. 22.1 Diseased saphenous vein graft (9 years post operatively) (left panel). Sequential left internal thoracic artery graft to the diagonal artery and to the left anterior descending artery (15 years post operatively) (right panel)

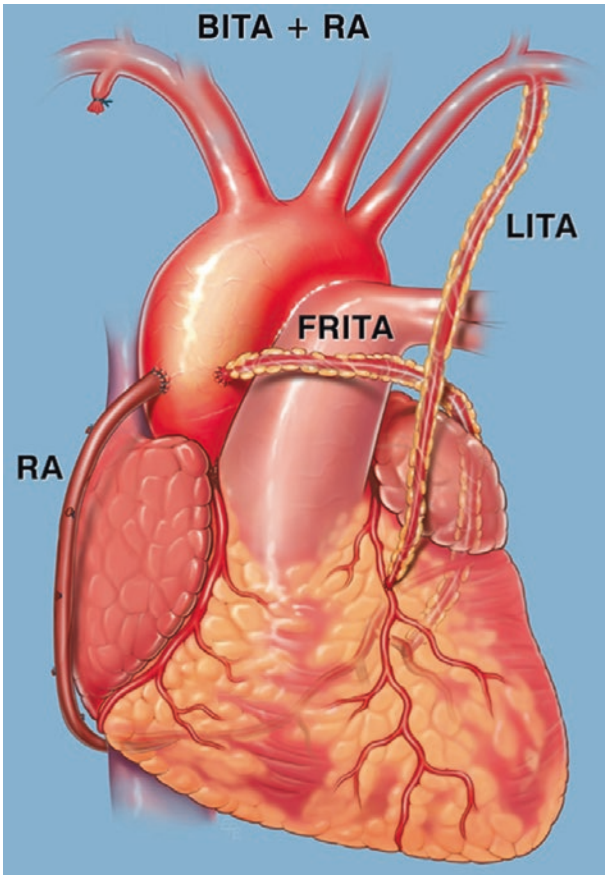

Fig. 22.2 Diagrammatic representation of an example of total arterial revascularization using bilateral internal thoracic arteries (BITA) with a left internal thoracic artery to the left anterior descending artery, a free right internal thoracic artery (FRITA) to the circumflex artery and a radial artery (RA) to the posterior descending artery

Currently, <5% of patients receive MABG in USA, 1–10% in Europe and 20–60% in Australia and Asia [3]. As life expectancy is increasing, 70–75-year-old patients—a common demographic in CABG can expect to live 15–17 years. Hence, operations that can deliver excellent outcomes over that time span are important [10]. SVGs, used for over 50 years comprise the majority of all coronary grafts. Procurement is by open or endoscopic technique. Although endoscopic vein harvesting (EVH) is associated with fewer wound problems, more SVG intimal and wall trauma in EVH leads to poorer patency rates and survival [4]. SVGs are not affected by the degree of native coronary artery stenosis (NCAS) [11].

Arterial Coronary Grafts

Left Internal Thoracic Artery (LITA)

The LITA is an elastomuscular artery, 3–3.5 mm diameter proximally, and 2.0–2.5 mm distally [12]. Universally accepted as the best coronary graft, it is resistant to atheroma with 95% patency at 10 years, and 90% patency at 20 years [6]. It is currently used in over 95% of CABG—almost exclusively to the LAD. The LITA may also be used preferentially to the circumflex system, with the right ITA to the LAD.

It is susceptible to spasm, (mechanical stimulation, and vasoconstrictors), but responsive to potent vasodilators. Its distal 2–3 cm is narrower, has more smooth muscle and is more spasmogenic. Avoidance of this segment, facilitates the

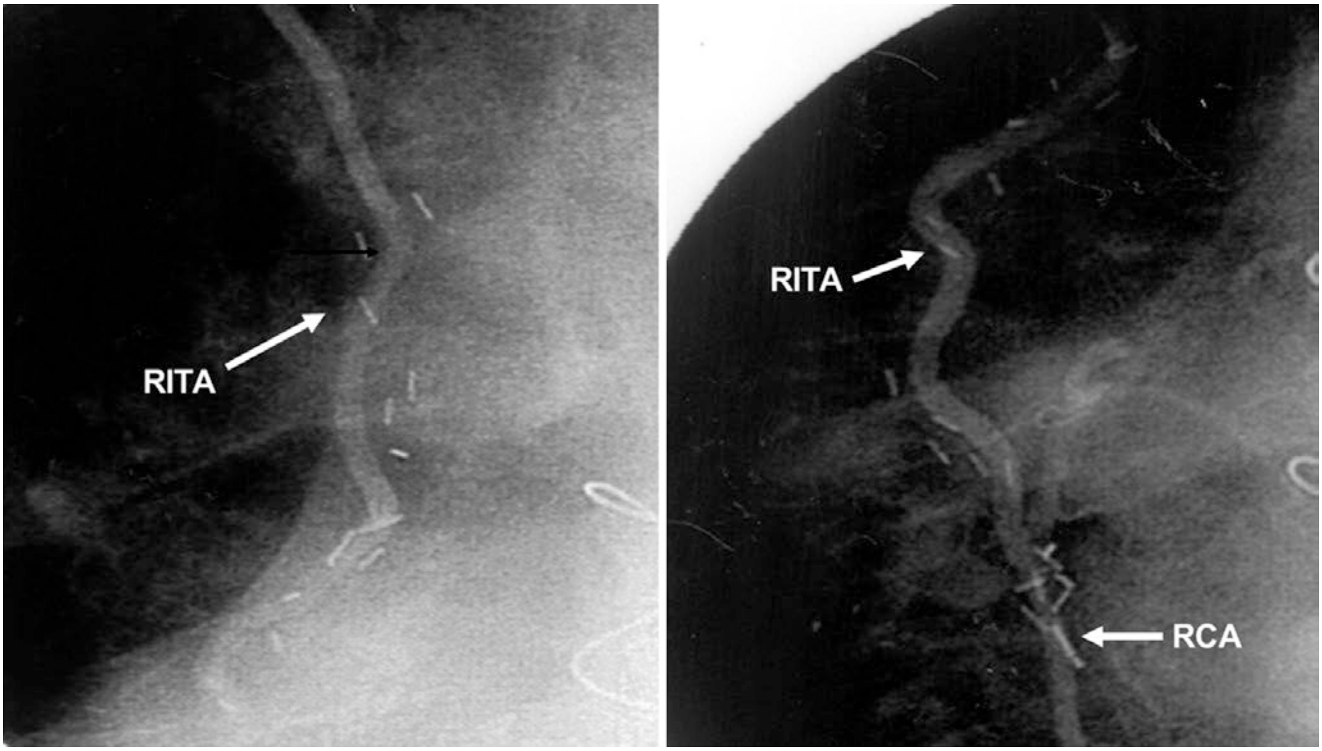

Fig. 22.3 In-situ right internal thoracic artery graft to the right coronary artery (11 years post operatively)

distal anastomosis, and enhances blood flow into the coronary [13]. The ITA may be harvested either as a pedicled or skeletonized conduit. The skeletonized technique results in better sternal vascularity, less dehiscence and infection [14]. The branches are divided with coronary scissors between small vascular clips, or by harmonic scalpel. The skeletonized ITA is usually 2–3 cm longer and dilates maximally with topical vasodilators [12].

Right Internal Thoracic Artery (RITA)

The RITA is biologically identical to the LITA. Harvest is identical to the LITA, and usually easier, as it is larger, and more separated from the IT vein, especially proximally (Fig. 22.3). Its use as an in-situ graft is limited. It will only reach the mid LAD, intermediate or proximal circumflex, the right coronary artery (RCA) near the acute margin and occasionally the proximal posterior descending (PDA) (Fig. 22.4).

Its use may be extended by construction of LITA-RITA Y grafts, RITA/RA extension grafts, or as a free graft (Fig. 22.5). Despite being an identical and superb ITA graft, its use is minimal. The reasons being non-familiarity, extra time required, concerns regarding sternal infection, hypoperfusion, and absence of evidence from randomized control trials (RCTs) [12].

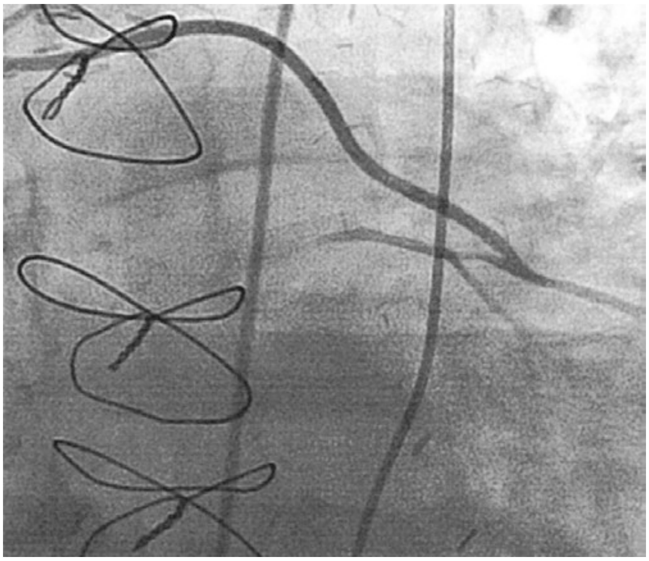

Fig. 22.4 In-situ right internal thoracic artery graft to the first obtuse marginal artery via the transverse sinus (15 years postoperatively)

Radial Artery (RA)

The RA is the second most commonly used arterial graft (approximately 10–20% of cases) [15]. Though first used in the early 70s, it was re-introduced after 1992 when early RA

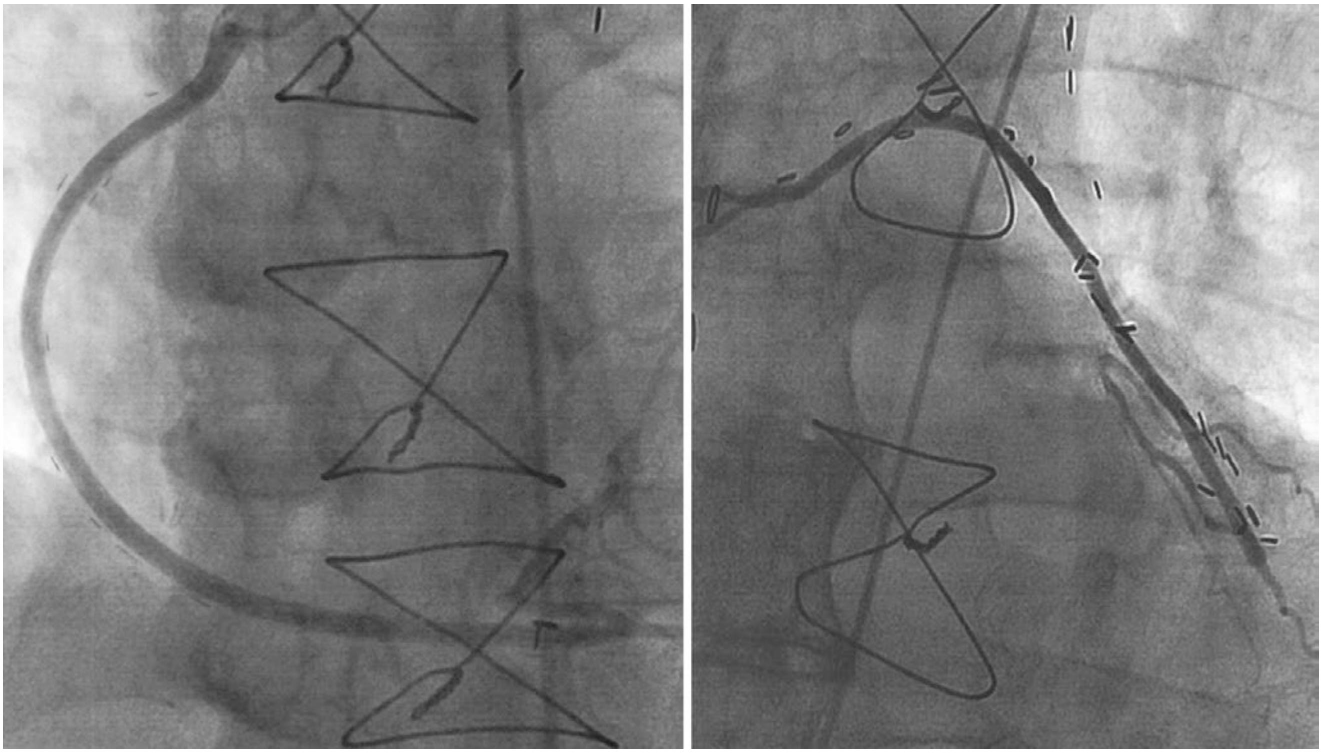

Fig. 22.5 Free right internal thoracic artery graft to the posterior descending artery (15 years postoperatively) (left panel) and to the mid circumflex marginal artery (12 years post operatively) (right panel)

grafts were shown to be patent 20 years later [16]. The RA is long (20–22 cm), versatile, robust, easy to handle and can be used identically to SVG. Distally its diameter is 2–2.5 mm, proximally 3–3.5 mm, an appropriate size for the coronaries. Assessment of ulnar collateral supply to the hand (adequate in 90–95%), by the modified Allen's test, or index finger pulse wave plethysmograph is mandatory [15, 17].

Harvest by open, or endo-harvest techniques produces equally good patency results [18]. The left RA, in a right handed patient, is harvested efficiently, concurrently with the LITA. It can be used as an aortocoronary graft, LITA-RA Y graft, or RITA-RA extension graft, is suitable for sequential anastomosis and can reach any coronary artery (Figs. 22.6 and 22.7).

The RA has a thicker, more muscular wall than the ITA, and is more sensitive to spasm. The RA transforms from a muscular to an elasto-muscular artery with a decrease in the smooth muscle components in its media, following implantation into the coronary circulation [19]. Spasm prophylaxis and avoidance of competitive flow are essential for successful RA use and excellent long term patency rates.

Contra indications to RA use include inadequate ulnar hand collaterals, severe calcification (usually distal third), small size (<2 mm), prior forearm trauma, A-V fistula for dialysis, collagen and Raynaud's disease, and recent instrumentation (angiogram and percutaneous Intervention) [15, 20].

Wound infection is rare. Sensory nerve dysfunction is not uncommon for up to 3–6 months, but hand power and dexterity is not affected. We have not experienced any hand or finger ischaemic symptoms in over 20 years [15].

Right Gastroepiploic Artery (RGEA)

The RGEA use is relatively rare, confined to some Asian and European centres. The RGEA has a muscular wall and is exquisitely sensitive to spasm. Harvest is accomplished by a 5 cm inferior extension of the sternotomy incision and facilitated by the harmonic scalpel. As for the RA, spasm prophylaxis, and avoidance of competitive flow is mandatory.

It is used as a further arterial graft, as a further source of inflow to the PDA, or distal RCA or when only the PDA requires grafting in redo surgery, allowing this to be performed off-pump, without re-sternotomy. Ten year patency results are reasonable—60%—though these also reflect the early learning curve, and lack of early knowledge about competitive flow [21].

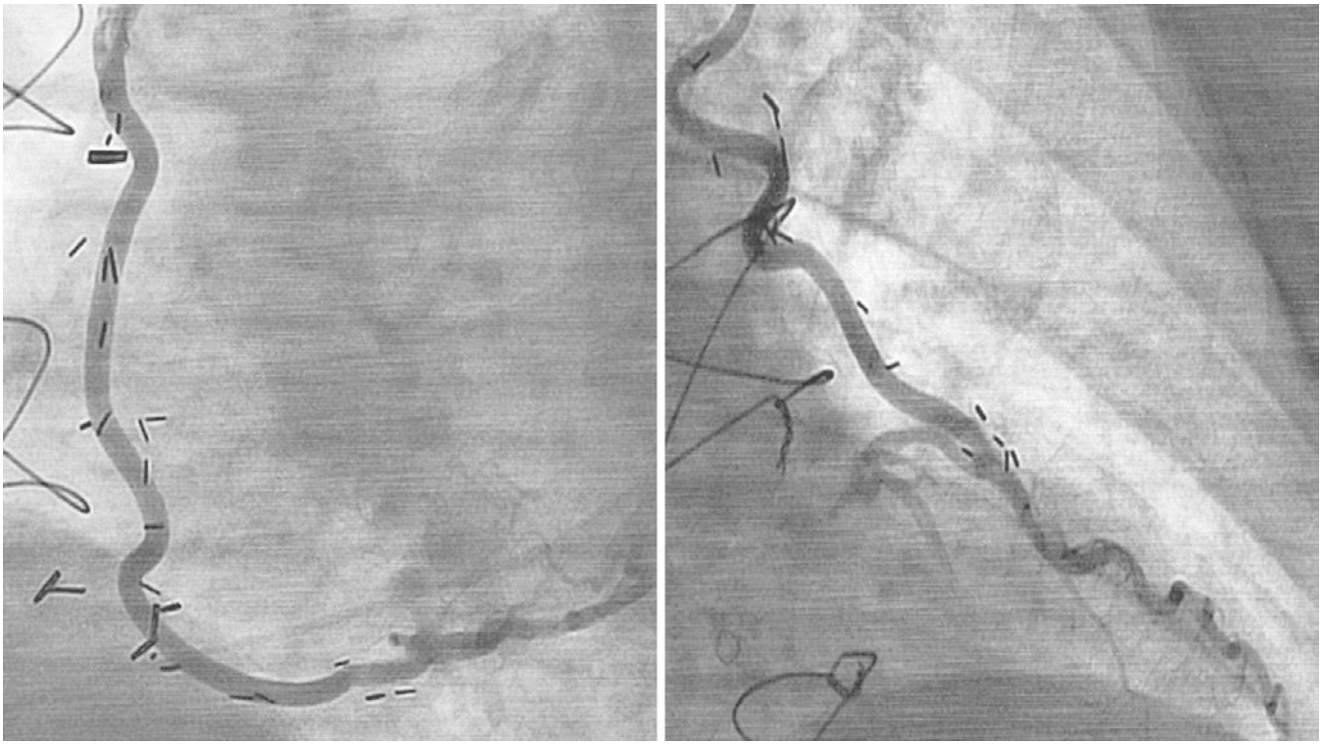

Fig. 22.6 Radial artery grafts to the posterior descending (left panel) and to the circumflex marginal artery (right panel) in the same patient (16 years post operatively)

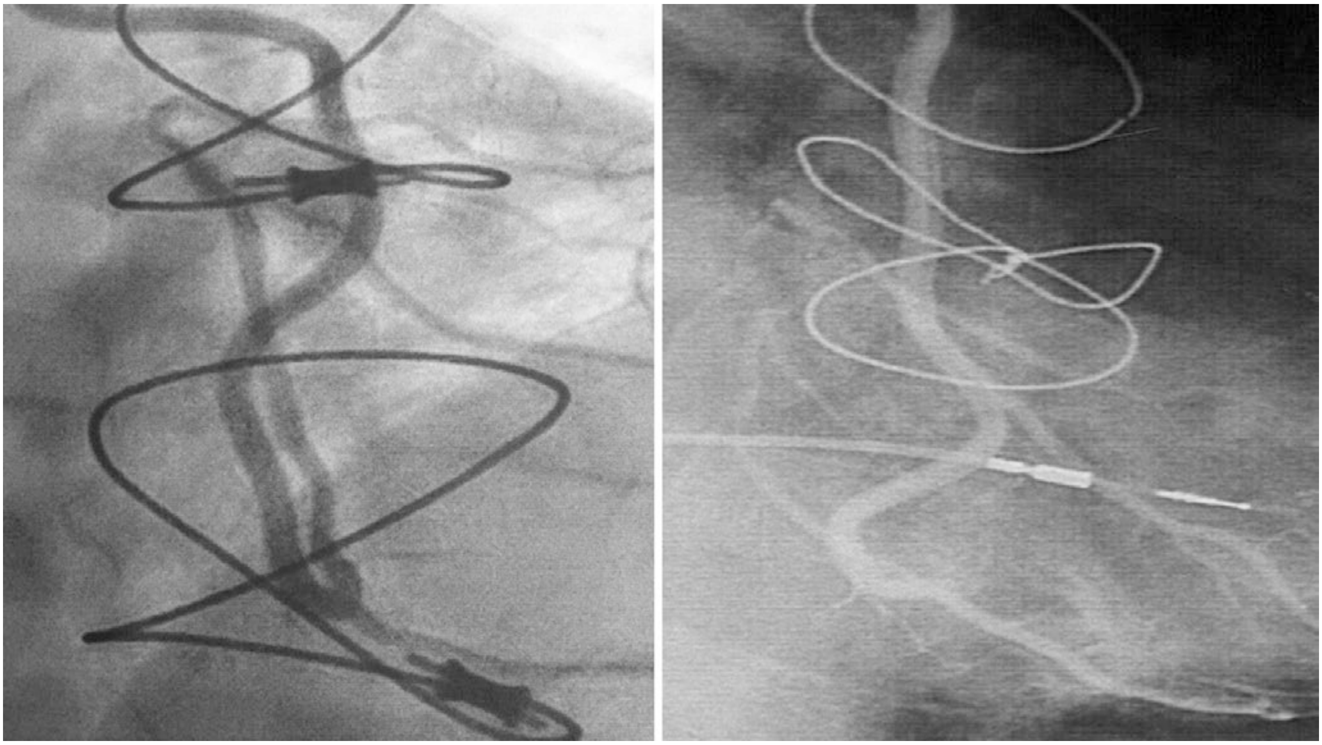

Fig. 22.7 Sequential radial artery graft to the mid and inferior circumflex marginal arteries (12 and 15 years post operatively respectively). Note: Smooth lumen in all of the arterial graft angiograms

Other Arterial Grafts

The inferior epigastric and ulnar arteries have been used. Both are muscular and have significant shortcomings. The inferior epigastric is short and could only be used as a short Y graft.

The ulnar artery is usually dominant, shorter than the RA and there is significant potential to damage the median nerve—a catastrophe.

Deployment Strategies to Achieve Total Arterial or Multiple Arterial Coronary Bypass Grafting

The LITA is placed to the LAD. The diagonal, if stenosed and medially placed, may be grafted sequentially “en-passant” via a side-to-side, parallel anastomosis. The LITA should be of a good size (diameter), must enter the pericardium proximally, preferably near its reflection off the pulmonary artery trunk, to ensure a smooth approach to the diagonal sequential anastomosis.

The RITA can be used in-situ, anterior to the aorta or through the transverse sinus to an intermediate or proximal circumflex marginal or to the RCA near the acute margin, if the RCA stenosis is proximal, and the distal RCA free of disease. Alternatively, as an aortocoronary free graft to the circumflex or PDA, and most commonly as a LITA/RITA bilateral internal thoracic artery (BITA) Y graft.

Bilateral Internal Thoracic Artery Grafts

The commonest format is for a LITA/RITA Y graft with the LITA to the LAD and the RITA revascularizing the circumflex system through multiple sequential anastomoses. If the RITA is of sufficient length and if there is no cardiomegaly, the PDA may also be grafted if required (Fig. 22.8). Alternatively, the PDA may be separately grafted with the RA, the RGEA, or an SVG.

If only the LAD and the proximal circumflex system require revascularization, that may be achieved with in-situ ITA grafts. A good size LITA (>2 mm) with good flow is essential for composite grafting.

Although the adequacy of inflow through one ITA to revascularize the entire left ventricle has been repeatedly validated, some surgeons feel uncomfortable, and prefer two or three separate inlet sources—LITA, RITA, further supplemented with an RA to either the distal RCA or distal circumflex.

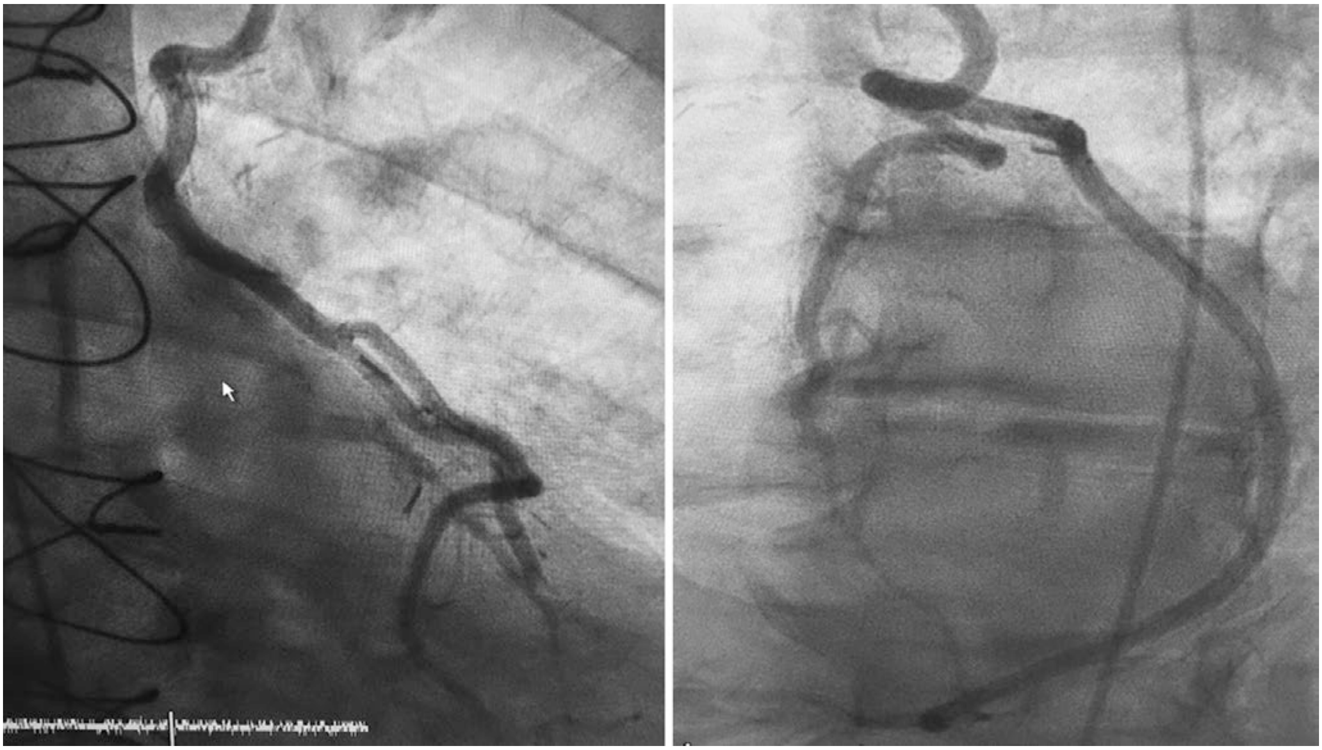

Fig. 22.8 Composite left internal thoracic artery (LITA) and right internal thoracic artery (RITA) Y graft. LITA to the left anterior descending artery, RITA to the circumflex artery (left panel) (16 years post operatively). Composite LITA and RA Y graft. LITA to the left anterior descending artery, RA to the inferior circumflex marginal artery (right panel) (18 years post operatively)

LITA and Left Radial Artery Graft

This is the commonest of all multi arterial grafting strategies. The LITA to the LAD and the RA graft to the circumflex (sequential graft), or, a LITA–RA Y graft [3, 15, 17–19, 22].

LITA and Bilateral Radial Arteries

If the right RA has not been instrumented, and there is paucity of conduit, or where leg veins are absent or legs need to be avoided, using both RAs allows TAR to be achieved. We commonly use this in older patients, in diabetics and in reoperations where venous grafts have failed, and/or have been used up. LITA and RA is a particularly useful strategy, as it is efficient, avoids sternal problems, and achieves MABG. The RA is an excellent graft for the circumflex marginals and the PDA [15, 17, 18, 22].

Equivalent patency and long-term results for the RA and RITA when used in similar situations have been reported, some favouring RA others the RITA [18, 22–24]. The overriding principle is to use the second arterial (and third arterial) graft to the next most important vessel(s). The LITA–RITA or LITA–RA Y graft strategies also facilitate anaortic off-pump CABG, which can also be achieved by LITA, and RITA/RA end to end extension. In turn anaortic CABG is associated with a much lower risk of stroke, especially in the elderly and very elderly as any manipulation of the aorta is avoided [25].

Anastomoses proximal to the RCA crux should be avoided unless the RCA wall is pristine as further occlusive plaque may develop at the crux over the next 5–10 years.

Arterial Graft Patency Rates

LITA patency rates (almost universally to LAD) are excellent—95% at 5 years, 90–95% at 10 years, and 85–90% at 20 years [2, 6, 12, 24, 26].

RITA and RA patency rates are not quite as good, but reflect their placement to non-LAD territories, i.e. to the circumflex marginals and PDA (unlike the LITA) [5, 6, 15, 16, 27].

A hierarchy of patency has always existed irrespective of conduit type where LAD graft patency rates are better than circumflex and in turn better than PDA or RCA. RITA and RA patency rates are similar, 85–90% at 10 years, and 85–88% at 20 years (especially if grafted to a tightly stenosed or occluded coronary artery) and are identical to the LITA when grafted to the same vessel, under the same circumstances [5, 6, 12, 15, 18, 24].

Arterial graft patency rates are always better than for SVG, irrespective of time frame and vessel grafted. These disparities become more pronounced with time [2, 5–7, 17, 24, 26, 27].

Table 22.1 summarizes conduit patency rates over time.

Table 22.1 Conduit patency rates at various time intervals postoperatively

Conduit	1 year	10 years	20 years
SVG	75–90%	50–60%	25–35%
LITA	95%	90–95%	90%
RITA	90–95%	90%	80–90%
RA	90%	85–90%	80–88%
RGEA	80–90%	60–70%	

SVG saphenous vein graft, *LITA* left internal thoracic artery, *RITA* right internal thoracic artery, *RA* radial artery, *RGEA* right gastroepiploic artery

A significant number of SVG patent at >10 years have advanced atheromatous changes

Clinical Results

Perioperative Results

Perioperative results for TAR and MABG are identical to those for LITA/SVG—1% peri-operative mortality, stroke 1%, MI and low cardiac output state 1–3%, intra-aortic balloon pump use 1–3%, reoperation for bleeding 1–3% [3, 5, 7, 8, 12, 15, 17, 18, 22–25]. Deep sternal wound infection (DSWI) rates are higher—3% versus 1% in BITA when pedicle grafts are used but identical at 1% if the ITAs are skeletonized [12, 14, 28, 29]. Hence fears of hypoperfusion, perioperative low cardiac output, MI, infection and mediastinitis are unfounded.

Long-Term Results

TAR and MABG confer clinical benefit and significantly superior long-term survival over LITA/SVG, noted in all observational and propensity matched studies with follow up of over 10 years [6, 7, 26, 30–33], and also recently in RCTs [34].

Survival and postoperative events (recurrent angina, MI, re-interventions, death), correlate with graft patency. Survival in both TAR/MABG, and LITA/SVG cohorts is similar and excellent for the first 5–7 years post-operatively. The survival curves then diverge. In general, 10 year survival for TAR/MABG is 80–88% versus 70–78% for LITA/SVG i.e. a 40–50% lower mortality, or alternatively 10 more patients, per 100 operated would be alive at 10 years if they had TAR/MABG as opposed to conventional LITA/SVG (Fig. 22.9).

Survival is also affected by age at surgery, left ventricular function, and co-morbidities, however, invariably TAR/MABG patients survive longer.

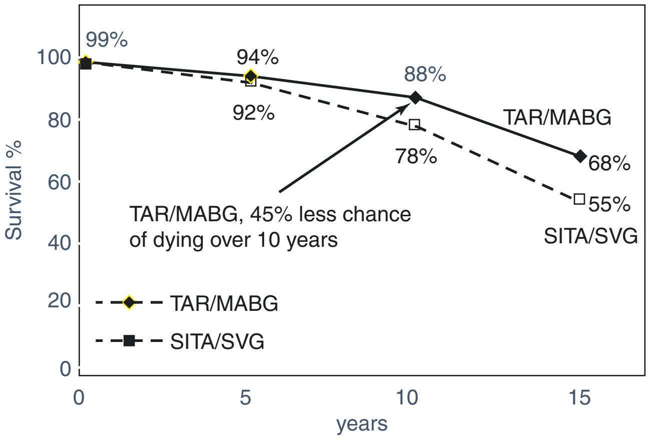

Fig. 22.9 Survival graph for total arterial (TAR) or multiple arterial bypass grafting (MABG) versus single internal thoracic artery and saphenous vein graft (SITA/SVG). Composite graph based on multiple published series

Although the randomized Arterial Revascularization Trial (ART) showed similar outcomes between BITA and Single ITA (SITA) at 5 years, the results were confounded by only a 5 year follow up, a high (14%) crossover from BITA to SITA, and multiple arterial grafts (23% additional RA) in the SITA group. When analyzed further for these confounders, ART patients that had multiple arterial grafts did better even at 5 years [29].

Longer term follow up studies (between 10 and 30 years) show progressively greater benefit for TAR/MABG [26, 31, 33, 35].

Three Versus Two Arterial Grafts

An ITA to the LAD is the most important revascularization strategy. The second arterial graft should be deployed to the second most important stenosed coronary—usually the circumflex marginal. There is controversy as to whether a third arterial graft, or TAR confers a significant additional prognostic benefit. Reports by the Melbourne group and others support the notion that three arterial grafts and TAR confirm additional prognostic benefit [36, 37]. A recent extensive meta-analysis reinforces this [38].

TAR/MABG also confers long-term survival advantage in a number of significant sub groups.

Elderly

As patients having CABG become older, the nature, and prognosis from the surgery becomes increasingly relevant. A 70-year-old in the Western world can expect to live a further 18 years (Australian Bureau of Statistics). Controversy exists regarding the role of TAR/MABG in this age group. Some report 72 years as the cut-off for further benefit from TAR/MABG [39], whereas others report benefits in the elderly and even very elderly [10, 25, 40]. Typical 10 year survivals are 68–70% for MABG/TAR versus 52% for LITA/SVG in propensity matched septuagenarians, and 60% versus 40% in patients over 80 years [40].

Gender

Men derive prognostic benefit from TAR/MABG [41]. The benefits in women have been less clear, confounded by later presentation, more advanced coronary disease, smaller vessels, and higher perioperative mortality and morbidity. Generally, women also show long term survival benefit within TAR/MAGB cohorts [41, 42].

Diabetes

40–50% of CABG patients have diabetes (approximately a third being insulin dependent)—a significant comorbidity [3, 43, 44]. The FREEDOM trial showed benefit for CABG over stents. Moreover, numerous large observational studies, and RCTs have shown additional survival benefit for TAR/MABG, as arterial grafts appear to be less affected by the diabetic process than SVG [43]. Typical 10 year survivals in diabetics are 80–85% for MABG/TAR versus 65–75% for LITA/SVG [43, 44].

The use of one or two skeletonized ITAs, in combination with RA can achieve TAR/MABG in diabetic patients. SVGs with lower patency rates and poorer prognosis, and leg wounds with their inherent complications can be avoided.

Chronic Renal Disease

Although chronic renal dysfunction is associated with a reduced life expectancy, nevertheless patients that require CABG (including those being considered for renal transplantation) do better prognostically with multiple arterial grafts—88% for MABG versus 77% for LITA/SVG at 5 years [45].

Left Ventricular Dysfunction

The large Kyoto cardiac surgery registry and the Surgical Treatment for Ischaemic Heart Failure (STICH) RCT both reported superior long term outcomes for CABG over percutaneous coronary intervention (PCI). Survival is further augmented by multiple arterial grafts. The degree of left ventricular dysfunction and extent of myocardial ischemic reversibility are major determinants of long term survival as well [46, 47].

Reoperations

In CABG reoperations, both RAs and the RITA are usually available. The best SVGs would have been used and failed thus requiring the re-intervention. Hence by necessity most patients that require a CABG reoperation will have multiple arterial grafts. The operative risk is 3–5%, and ironically there may be a better longer-term outcome from the reoperation with 3-year survivals of 89% [48, 49].

Off-Pump and Anaortic Coronary Artery Bypass Grafting

TAR/MABG techniques are suited to off-pump CABG, using LITA–RITA and LITA–RA Y grafts or LITA/RITA–RA extension grafts. Generally, all parts of the heart can be revascularized by one of these techniques, with complete avoidance of the aorta. Anaortic off-pump CABG can produce excellent results with operative mortalities of <1%, and stroke <1% in both the elderly, and in octogenarians [25].

Conversely, it is counterintuitive to perform off-pump CABG as a "less invasive" procedure but use SVGs and side-biting clamps which may risk a higher stroke rate and a higher likelihood of future reoperations. Off-pump CABG with a majority of SVG conduits requires immediate dual antiplatelet therapy—an acknowledgement of a higher incidence of SVG thrombosis.

Contraindications and Limitations of Total Arterial or Multiple Arterial Coronary Bypass Grafting

Arterial conduits should be of good size, have good flows, and be free of plaque. ITA harvest trauma is not uncommon. A RA <2 mm diameter distally is contraindicated. Severe RA wall calcification, sometimes seen distally, may distort and make a distal coronary anastomosis difficult and not hemostatic [15].

Deeply intramyocardial coronaries make sequential grafting difficult. Cardiomegaly should be noted with respect to graft lengths. Bilateral ITAs should be avoided in morbidly obese, insulin-dependent, diabetic patients, those with severe chronic obstructive airways disease and where there has been prior chest radiation. Such patients can still have TAR/MABG using one ITA and one or two RAs [12, 15, 18, 22, 43, 44].

An instrumented RA (angiogram or PCI), should be avoided, at minimum, a 3-month delay is recommended. Such an RA is often partly dissected, is less vasoresponsive to both vasoconstrictors and vasodilators, and is associated with lower patency [20].

Role of Saphenous Vein Grafts

In emergency CABG, it is logical to use LITA/SVGs to achieve rapid revascularization. Occasionally, this may necessitate harvesting the LITA after institution of cardiopulmonary bypass. Additionally, if the RA or RITA cannot be used—calcification, inadequate ulnar collateral hand supply, and where long-term prognosis may be limited (neoplasms)—then SVGs are the conduits of choice. Some surgeons may also use SVGs to supplement two arterial grafts.

We prefer SVGs from the lower leg (ankle to knee) as this segment has a normal wall, uniform size, with few or no branches and valves and has excellent mid-term patency [24]. Recent reports have shown very good to excellent mid-term SVG patency rates when used as LITA–SVG Y graft [50], or when harvested with a no touch technique with the adjacent perivascular and subcutaneous tissue [51] or external support [52].

Controversies in Total Arterial and Multiple Arterial Coronary Bypass Grafting

What is the best approach to myocardium known to be infarcted? An arterial graft? An SVG? A stent? Or nothing at all? Myocardial reversibility studies could be helpful, but unfortunately there is little evidence in this area.

The role of fractional flow reserve (FFR) is also unclear. Evidence exists for the efficacy of PCI when the FFR is <0.80. It is intuitive to use this threshold measurement for CABG as well, but there is little information to validate and support this.

The approach to moderate coronary stenoses is also unclear. Definitions of "moderate" vary, as do their impact within different size arteries. Internal diameter at the most stenotic point is a better objective parameter, but is rarely measured, and not documented in retrospective datasets. Moderate circumflex stenosis (>70%) should be bypassed. However, it is unwise to use arterial grafts for moderate RCA stenoses, as the relative restriction to coronary flow may be minimal, and the arterial graft significantly affected by competitive flow. In addition, moderate RCA stenoses progress slowly [53]. In young patients we would leave such stenoses alone, monitor closely, and consider a stent in the future. For older patients (>70 Years), we would use an SVG, particularly if the distal RCA territory was large.

Conclusion

Total or multiple arterial CABG is feasible for most patients. Important caveats are spasm prophylaxis, and avoidance of competitive flow. It can be achieved with similar perioperative results to conventional CABG, but importantly, results in superior long-term graft patency and patient survival, evident 10 years postoperatively, even in patients with significant co-morbidities. It has the potential to markedly improve the quality and length of CABG patients' lives and should be considered for a greater proportion of patients undergoing CABG.

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23

Anastomotic Devices for Coronary Artery Surgery

Nirav C. Patel and Jonathan M. Hemli

High Yield Facts

- Anastomotic devices can facilitate the rapid construction of reproducible, compliant anastomoses, naturally complementing off-pump and minimally-invasive coronary grafting procedures.
- Proximal anastomotic devices are neuroprotective; multiple studies have demonstrated that their use is associated with a reduced risk of perioperative stroke, in parallel with their ability to minimize the degree of aortic manipulation required intraoperatively.
- The Heartstring Proximal Seal System is not, in itself, an automatic anastomotic connector; it enables the surgeon to construct a hand-sewn aorto-graft anastomosis while obviating the need for an aortic clamp (concomitantly reducing the risk of adverse neurological outcome).
- The PAS-Port Proximal Anastomosis System automatically constructs a completed aorto-graft anastomosis; the surgeon is no longer required to hand-sew the anastomosis.
- The C-Port Distal Anastomosis Systems are the most commonly utilized distal anastomotic devices and can aid in rapidly constructing a compliant coronary anastomosis in difficult-to-reach areas of the surgical field.
- The safety and efficacy of all these devices have been demonstrated in multiple clinical studies, and the patency of the grafts that they construct are not inferior to traditional hand-sewn grafts, at least in the mid-term.

Introduction

The risk of stroke after coronary artery bypass grafting (CABG) is one of the main arguments used by the proponents of percutaneous intervention (PCI), despite strong evidence supporting the superiority of CABG over PCI for multi-vessel disease [1–5].

Although there is continued debate as to the relative merits of off-pump coronary artery bypass (OPCAB), as compared with traditional on-pump CABG, most authorities concur that the benefits of off-pump surgery include greater flexibility to reduce the incidence of perioperative stroke in those patients deemed to be at higher intrinsic risk for adverse neurologic outcomes (Table 23.1). There are a multitude of factors that contribute to perioperative neurologic injury in coronary surgery, yet there is no doubt that minimizing manipulation of the ascending aorta is directly neuro-protective [6]. The use of proximal anastomotic devices can significantly reduce the degree of aortic manipulation required to fashion a graft based on aortic inflow, and, importantly, can dispense with the need for aortic clamping altogether.

However, eliminating perioperative neurologic complications, whilst a vital and noble goal, is no longer sufficient, in

Table 23.1 Variables associated with higher risk of perioperative stroke in coronary artery bypass surgery

Risk factors associated with stroke in coronary surgery
Age greater than 70 years
History of prior stroke or TIA
Radiographic evidence of prior stroke on CT or MRI
Carotid artery stenosis greater than 70% (bilateral > unilateral)
Peripheral vascular disease
Atrial fibrillation
Moderate to heavy calcification in the ascending aorta identified on preoperative imaging Significant atheroma identified in the aortic arch and/or descending thoracic aorta on intraoperative TEE
Preoperative creatinine greater than 2 mg/dL (176.8 μmol/L) and/or dialysis-dependent renal failure

TIA transient ischemic attack, *CT* computed tomography, *MRI* magnetic resonance imaging, *TEE* transesophageal echocardiography

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and of itself, to bolster the role of CABG in the current era of ever-improving drug-eluting stents. The surgeon must now be able to offer options for minimal-access and non-sternotomy revascularization, while still being able to complete the perfect anastomosis, irrespective of the challenges presented due to limited access. Proximal and distal anastomotic devices are ideally suited for this purpose: they can facilitate the rapid creation of a reproducible, compliant anastomosis, off-pump, in a difficult-to-visualize operative field, through a small incision, avoiding a sternotomy, or even totally endoscopically inside the closed chest [7].

A number of different proximal and distal anastomotic devices incorporating an array of diverse technologies have been introduced over the years, although, for various reasons, the majority have since been discontinued and are no longer available.

Proximal Anastomotic Devices

Heartstring Proximal Seal System

The Heartstring Proximal Seal System (Getinge Group, Wayne, NJ), now in its third iteration (Fig. 23.1), facilitates a hand-sewn anastomosis between the aorta and a bypass conduit, obviating the need for an aortic clamp. If the aorta is heavily calcified, epiaortic ultrasound is useful to identify a relatively disease-free site for the intended anastomosis. If the anastomotic target area is not on the absolute anterior surface of the ascending aorta, a number of maneuvers have been described that can be helpful in improving exposure [8].

To use the Heartstring III system (Fig. 23.2), the proximal aortic seal is loaded into the delivery device and advanced forward, appropriately shaping it to facilitate its subsequent atraumatic passage into the aorta. After the delivery device is removed from the holder, the lock is disengaged, and the seal is ready to be deployed, after an aortotomy has been fashioned using the cutting tool. We do not use the Heartstring with an aorta less than 18 mm in diameter, as the posterior wall of a small aorta may potentially be at risk of being damaged by the cutter, and, for the same reason, we also ensure that the systolic blood pressure is greater than 70 mmHg at the time of device deployment (mean pressure should be at least 55 mmHg). The Heartstring proximal seal does not provide a completely hemostatic aortic plug; we utilize a humidified carbon dioxide mister-blower to keep the anastomotic area relatively free of blood to enable accurate suture placement. Alternately, a fine-tip suction catheter can be used to scavenge any excess blood.

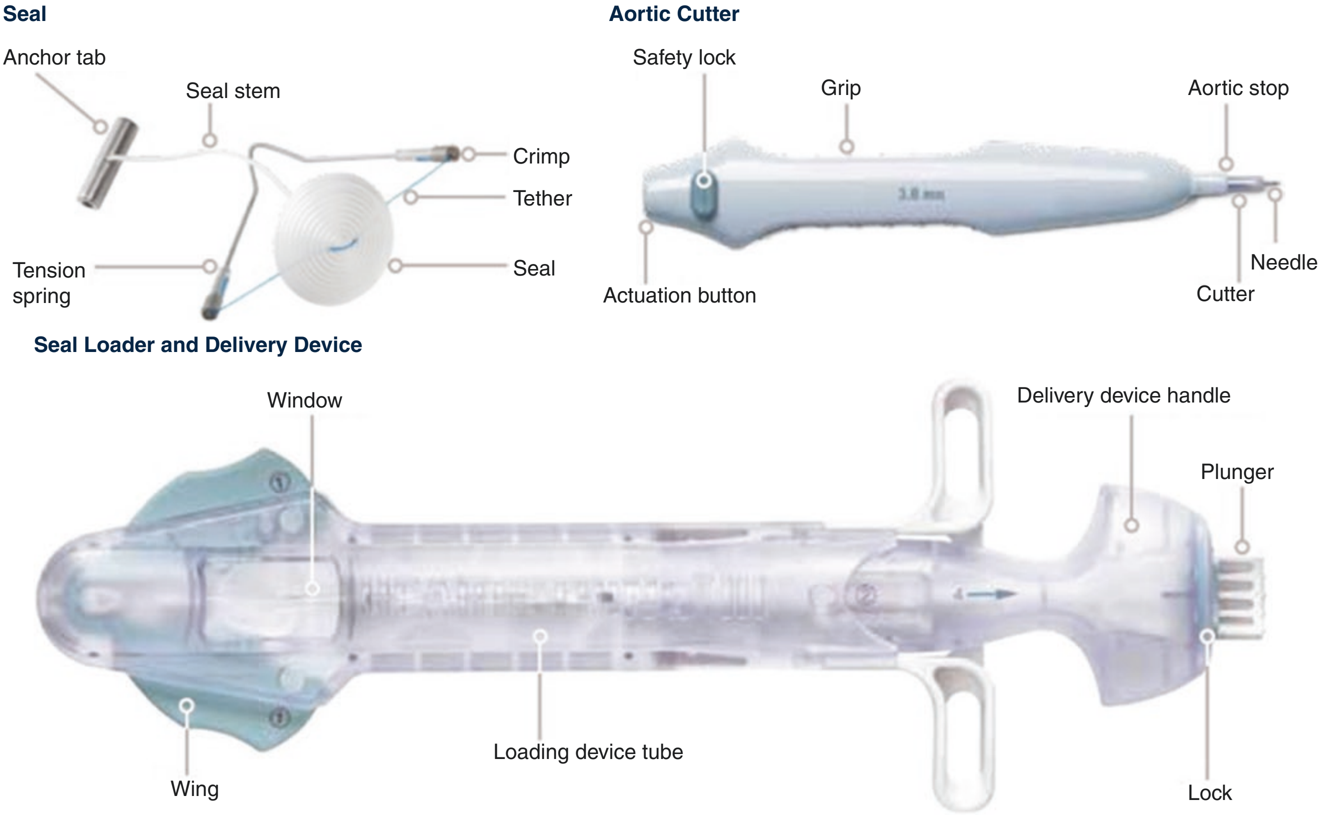

Fig. 23.1 The components of the Heartstring III proximal seal system. (*Courtesy of Getinge Group, Wayne, NJ*)

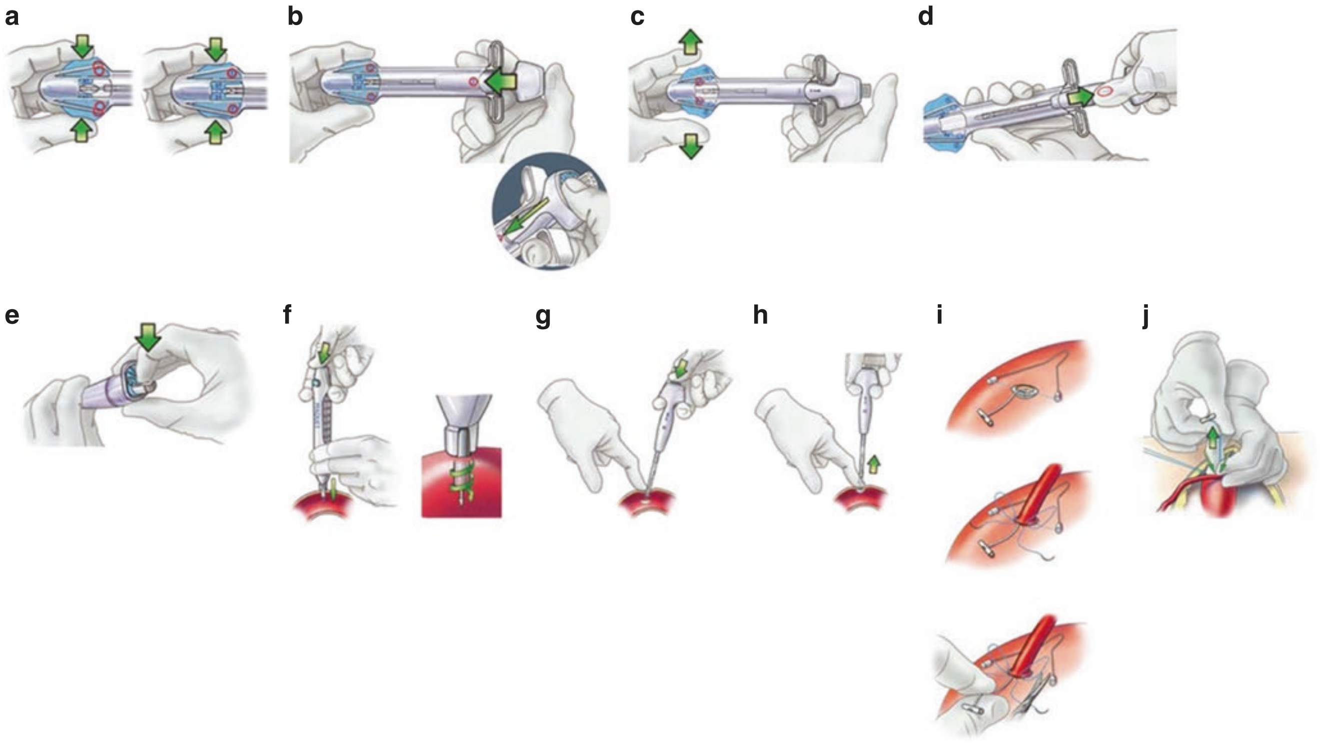

Fig. 23.2 Deploying the Heartstring III proximal seal system. (**a**) the two blue wings at the end of the loading instrument are squeezed together; (**b**) the delivery device is advanced into the loading system; (**c**) the blue wings are released; (**d**) the delivery device is pulled out of the loading instrument; (**e**) the delivery device is unlocked by releasing the white catch and is now ready for use; (**f**) the aortic cutter is stabilized perpendicular to the aorta, the gray actuation button is depressed to create the aortotomy, and the aortotomy is covered by the surgeon's finger after the cutter has been removed; (**g**) the delivery device is slid into the aorta, underneath the surgeon's finger, and the white plunger is depressed, deploying the seal into the aorta; (**h**) the delivery device is removed, the surgeon's finger still covering the aortotomy until the tension spring is fully open and the seal is in place; (**i**) the aorto-conduit anastomosis is fashioned, using an inside-out technique on the aorta to minimize the risk of inadvertently catching the edge of the seal with the suture; after the last suture has been completed, the tether holding the tension spring is released, and the tension spring is removed; (**j**) the intra-aortic seal is removed and the anastomosis is tied. (*Courtesy of Getinge Group, Wayne, NJ*)

The neuro-protective effects of using the Heartstring system to avoid aortic clamping have been well described. Emmert and associates reviewed 2203 OPCAB patients and reported rates of stroke of 2.3% in those patients in whom a partially-occluding aortic clamp was used to facilitate construction of the proximal anastomoses, 0.7% in that cohort of patients in whom the Heartstring was utilized, and 0.8% in those in whom the ascending aorta was not handled at all [9]. The authors concluded that not only does the use of the Heartstring significantly reduce the incidence of stroke during OPCAB *vs.* the use of an aortic clamp, but that it may actually result in an overall stroke risk that is comparable to that of a procedure in which the ascending aorta is not manipulated at all. Similarly, more recently, Formica and colleagues evaluated 282 OPCAB patients who utilized the Heartstring device and found no significant differences in their stroke rate as compared to that of a concurrent group of 363 patients who underwent a complete no-aortic-touch operation [10].

Hilker and associates utilized the Heartstring system during 542 proximal anastomoses in 412 OPCAB cases, reporting an overall incidence of postoperative stroke of 0.48%, significantly better than the 1.37% that was predicted for their patient cohort by established stroke risk models [11]. Sakopoulos and co-workers employed the Heartstring in 227 OPCAB patients and witnessed no clinically evident adverse perioperative neurologic events, despite a preoperative incidence of cerebrovascular disease of over 20% in their study population [12]. Douglas and Spaniol documented a stroke rate of 0.8% in their OPCAB patients who had proximal anastomoses constructed using the Heartstring device, despite the presence of severe aortic disease in the majority of these individuals, confirmed by epiaortic ultrasound [13]. Wilhelm and colleagues used the Heartstring to construct 442 proximal anastomoses in 260 OPCAB procedures, reporting perioperative stroke in only two patients (0.8%) [14]. A meta-analysis of the use of the Heartstring system analyzed 819 patients across eight studies; only six patients overall (0.7%) sustained a perioperative stroke [15].

El Zayat and colleagues randomized 57 OPCAB patients to have their proximal anastomoses constructed either with the use of a partially-occluding aortic clamp or with the Heartstring device [16]. Despite the low incidence of aortic atherosclerosis in the patients included in this study, those in the Heartstring group still had significantly less cerebral microemboli, as detected by transcranial Doppler, than did those in whom the clamp was utilized, suggesting a potential benefit for the clampless technique even in those patients who do not have a hostile ascending aorta. Moreover, the burden of cerebral microemboli was still lower when a suction device was used to scavenge the excess bleeding around the proximal seal of the Heartstring, as opposed to employing the humidified mister-blower, a finding also confirmed by others [17, 18].

The safety profile of the Heartstring is well documented [19], with few published adverse outcomes, although type A aortic dissection has been described [20], emphasizing the importance of strict blood pressure management when the aortotomy is being made, as well as ensuring that the device is wholly within the aorta prior to deployment of the seal.

PAS-Port Proximal Anastomosis System

Unlike the Heartstring, which is a device that facilitates a clampless hand-sewn anastomosis, the PAS-Port Proximal Anastomosis System (Aesculap AG, Tuttlingen, Germany) is a truly automated proximal anastomotic connector (Figs. 23.3, 23.4 and 23.5). The instrument not only dispenses with the need for the aortic clamp, but the surgeon is also no longer required to manually suture the graft to the aorta. The device is thus useful not only in those cases where the primary aim is neuro-protection, but it is also beneficial in minimal-access cases, where the aorta may be relatively remote from the surgical field, making it that much more challenging to fashion a hand-sewn anastomosis.

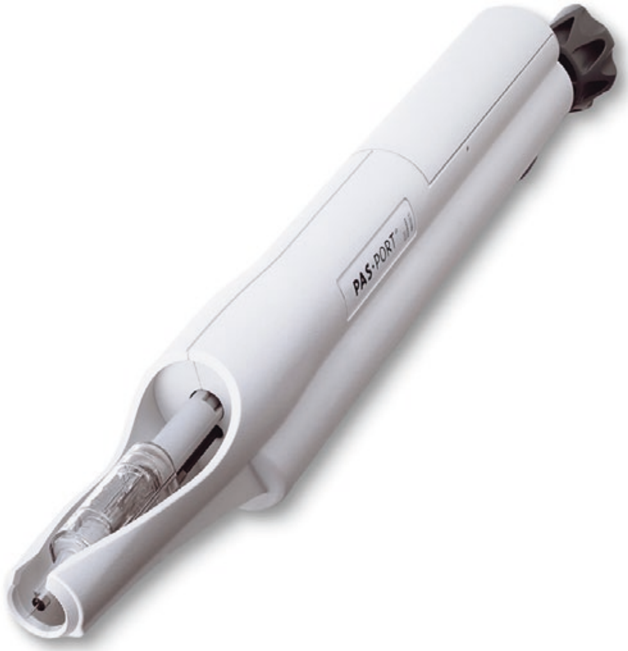

Fig. 23.3 The PAS-Port proximal anastomotic connector and its components. (*Courtesy of ©AESCULAP AG, Tuttlingen, Germany*)

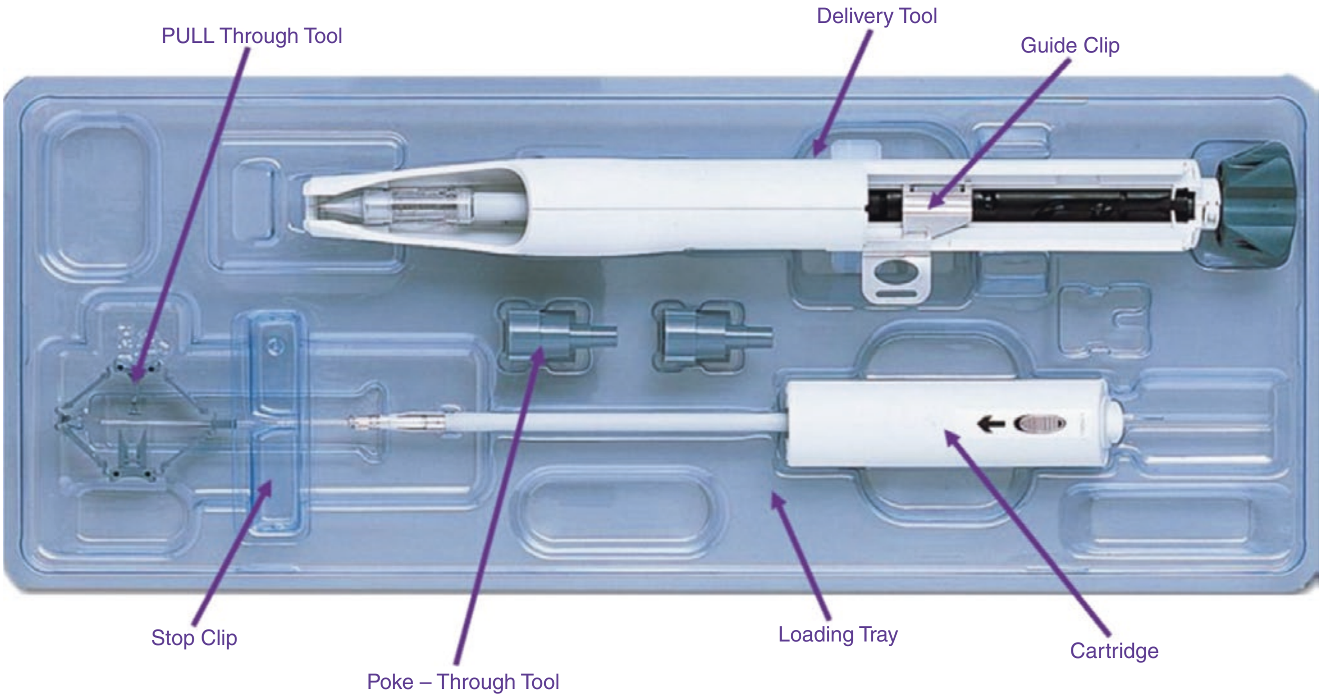

Fig. 23.4 The PAS-Port proximal anastomotic connector and its components. (*Courtesy of ©AESCULAP AG, Tuttlingen, Germany*)

Use of the PAS-Port system necessitates completion of the proximal anastomosis prior to construction of the distal coronary anastomoses. Not all harvested veins, however, are suitable to be used with the PAS-Port system; the vein should be between 4 and 6 mm in external diameter, and the double wall thickness of the vein, when flaccid, should be no more than 1.4 mm. The harvested vein is attached to the hook of the device, pulled through the cartridge to emerge at the other end, and then positioned, such that 3–6 mm of vein remains exposed through the delivery cartridge. The edges of the vein are everted over the device itself and then manipulated until all tines are visible and evenly exposed. The PAS-Port delivery device is positioned perpendicular to the target area on the aorta and activated (Fig. 23.6). A successfully deployed graft comes off the aorta at 90°, has no kinking, has an everted edge, and has very little blood-exposed non-intimal surface (BENIS) (Fig. 23.7). Given the PAS-Port's ability to automatically, rapidly, and reliably construct an

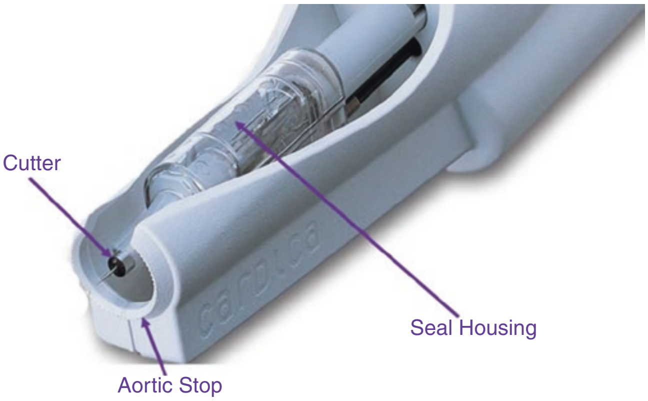

Fig. 23.5 The PAS-Port proximal anastomotic connector and its components. (*Courtesy of ©AESCULAP AG, Tuttlingen, Germany*)

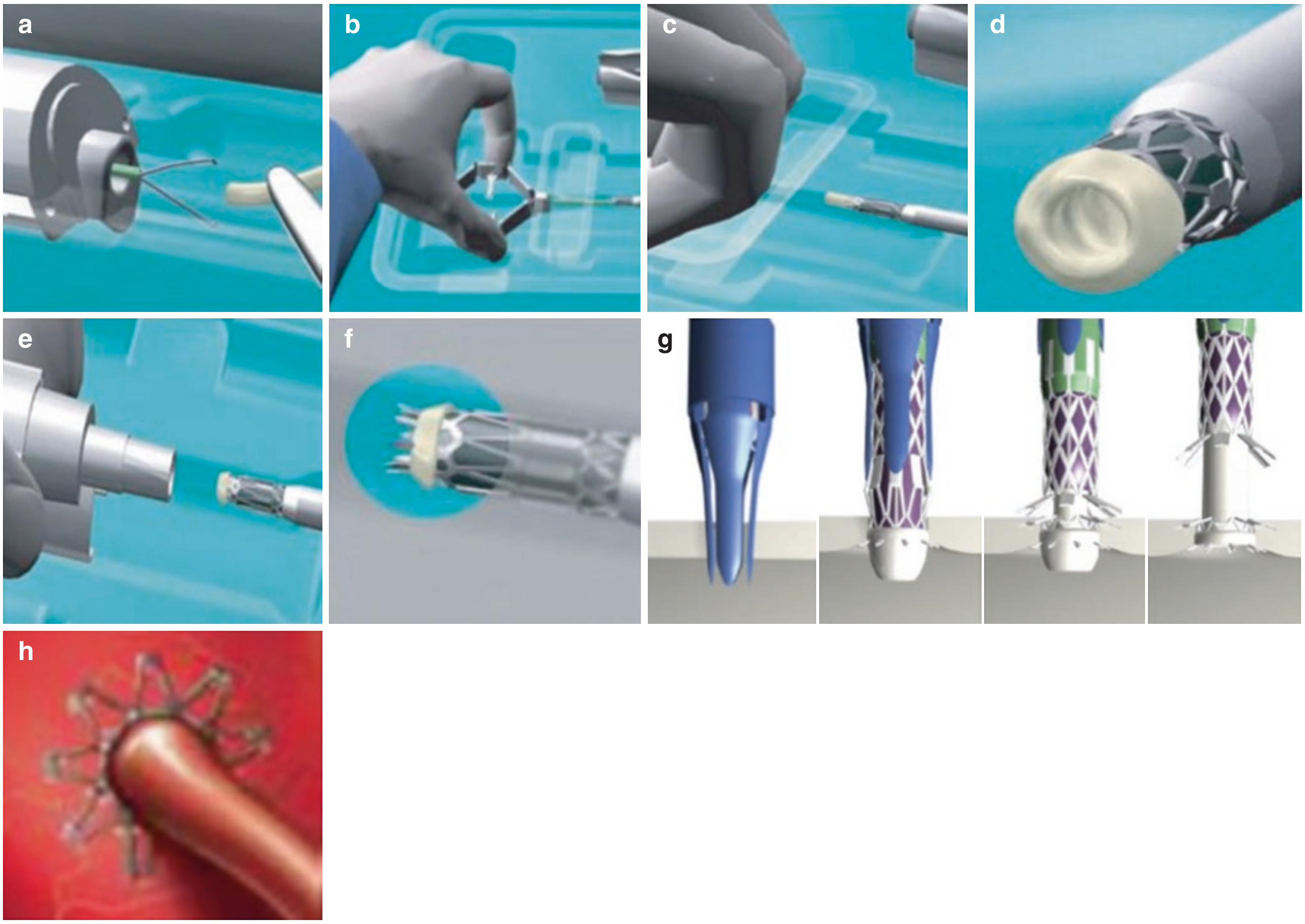

Fig. 23.6 Utilizing the PAS-Port proximal anastomotic device. (**a**) the proximal end of the harvested vein is grabbed by the hook of the device; (**b**) the vein is pulled through the instrument; (**c**) 3–6 mm of vein is exposed at the end of the cartridge; (**d**) the edges of the exposed vein are trimmed and symmetrically everted; (**e**) the 'poke-through' tool is utilized to pierce the everted vein, exposing the tines; (**f**) all tines are visibly and evenly exposed; (**g**) the device is positioned perpendicular to the aorta and activated, automatically creating the anastomosis, and the vein graft is subsequently teased out of the delivery cartridge; (**h**) the successfully deployed graft comes off the aorta without kinking. (*Courtesy of ©AESCULAP AG, Tuttlingen, Germany*)

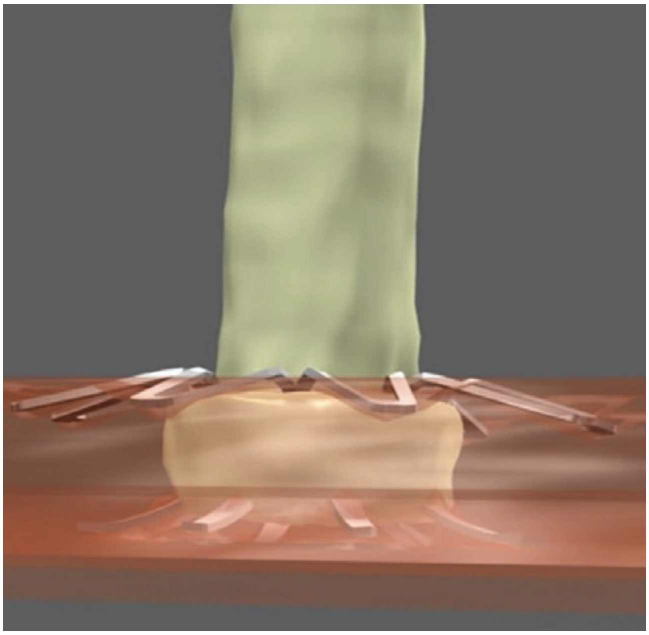

Fig. 23.7 Completed aorta-vein graft anastomosis with the PAS-Port device. (*Courtesy of ©AESCULAP AG, Tuttlingen, Germany*)

aorto-coronary anastomosis, with minimal aortic handling, we routinely use the device in those cases where the hostility of the aorta may even preclude the use of the Heartstring, a strategy that has been echoed by others [21]. Reports of using the PAS-Port device with radial artery as conduit have also been described [22].

Puskas and associates evaluated the efficacy of the PAS-Port system in a multicenter, prospective randomized trial (EPIC) [23]. The 9-month angiographic patency of those grafts created by the PAS-Port device (80.3%) was not significantly different to that of a concurrent group of hand-sewn grafts (82.0%), and the freedom from major adverse cardiac events (MACE) was similar for the two groups. Demertzis and colleagues analyzed 101 PAS-Port generated anastomoses in 86 patients, assessed either by CT or by invasive angiography, and documented a 6-month patency rate of 88% [24]. Verberkmoes and associates found no significant difference in coronary reintervention rates at 36 months follow-up in 201 patients who had their anastomoses fashioned by the PAS-Port system, as compared with 111 patients who had more traditional proximal anastomoses [25].

Kempfert and co-workers randomly assigned 99 OPCAB patients to receive either hand-sewn proximal anastomoses or PAS-Port generated grafts, and found a trend towards a lower rate of delirium in the PAS-Port group (11.7%) as compared with the hand-sewn group (25%) [26]. Patency of the PAS-Port grafts, assessed by CT angiography, was 100% at hospital discharge, and was 97.8% at 1-year follow-up. Borgermann and colleagues reported significantly reduced rates of stroke and in-hospital death in over 1000 coronary patients in whom the operation was completed off-pump and totally clampless, either with the use of the PAS-Port, or utilizing a true no-aortic-touch technique [27]. Favorable results with the PAS-Port device have also been similarly confirmed by a number of other investigators [28–31].

Distal Anastomotic Devices

C-Port Distal Anastomosis System

The primary commercially available distal anastomotic device currently in general use is the C-Port Distal Anastomosis System (Aesculap AG, Tuttlingen, Germany), with either a rigid shaft (C-Port xA) (Fig. 23.8) or a flexible shaft (C-Port Flex-A) (Fig. 23.9). The C-Port system is designed to facilitate a rapid, automated, end-to-side coronary anastomosis between a conduit and a native coronary artery, essentially replacing the need to hand-sew a traditional graft. The device secures the graft to the target artery with multiple, independent, stainless steel staples, resulting in a compliant anastomosis that can be quickly and reproducibly recreated. We originally used the C-Port system to graft smaller, diffusely diseased, difficult-to-reach branches of the circumflex artery in off-pump procedures. We have now liberalized its use to other cases, and its potential for use in minimal-access and robotically-assisted endoscopic coronary surgery is also clear.

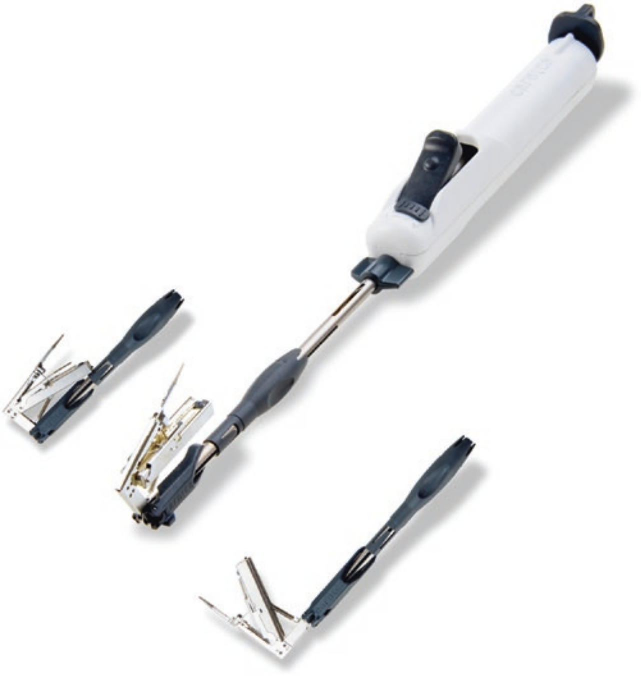

Fig. 23.8 The C-Port xA (rigid shaft) distal anastomotic device. (*Courtesy of ©AESCULAP AG, Tuttlingen, Germany*)

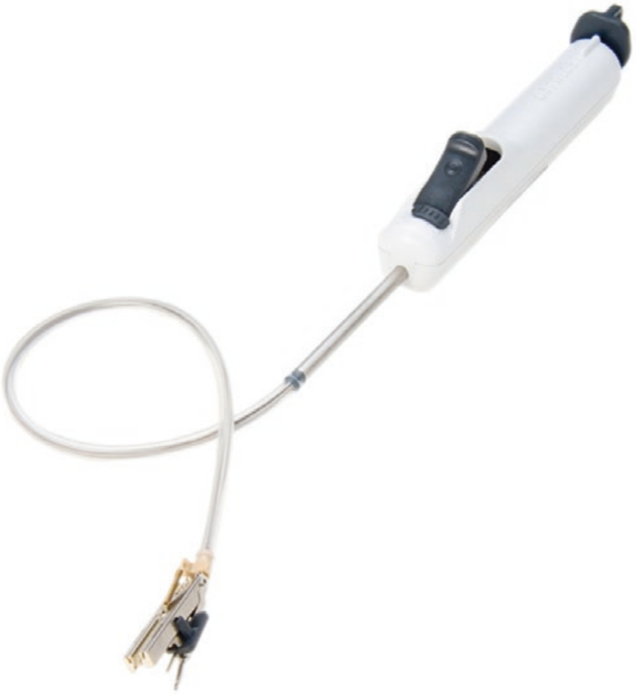

Fig. 23.9 The C-Port Flex-A (flexible) distal anastomotic device. (*Courtesy of ©AESCULAP AG, Tuttlingen, Germany*)

The heel of the harvested vein is positioned within the arms of the C-Port cartridge and punctured by the spike of the instrument. The vein is triangulated, such that the body of the graft is pulled downwards, while the edges of the vein are everted and secured within the arms of the system. The vein shield is lowered into the hood of the graft to protect it from being incised by the blade when the arteriotomy is made in the target coronary artery (Fig. 23.10). A 7′0 prolene suture is used to fashion a small purse-string passing very superficially through the native coronary vessel at the intended location of the heel of the anastomosis. The coronary artery is sharply incised in the center of this purse-string suture, a 1 mm coronary probe is passed distally into the vessel to ensure uninterrupted passage for the C-Port device, and the anvil of the system itself is then introduced into the artery. The device is fired, constructing the anastomosis. The CO_2-powered cartridge automatically creates an arteriotomy in the target coronary artery and secures the graft to the vessel with individual staples without interrupting native coronary blood flow, thus avoiding the need for intracoronary shunts and obviating any myocardial ischemia. The device is withdrawn and the purse-string suture is tied. The end-result anastomosis has minimal BENIS, and all intimal components of the vein graft that had been physically handled are excluded from the actual anastomosis itself (Fig. 23.11).

The safety and efficacy of the C-Port device was initially assessed in a prospective, non-randomized, multicenter trial, the results of which were reported by Matschke and coworkers [32]. Of 107 C-Port anastomoses that were studied at hospital discharge, 106 (99.1%) were found to be patent. At 6-months follow-up, 98 C-Port anastomoses were assessed by either invasive angiography or by CT, and the overall FitzGibbon A patency for those grafts evaluated by

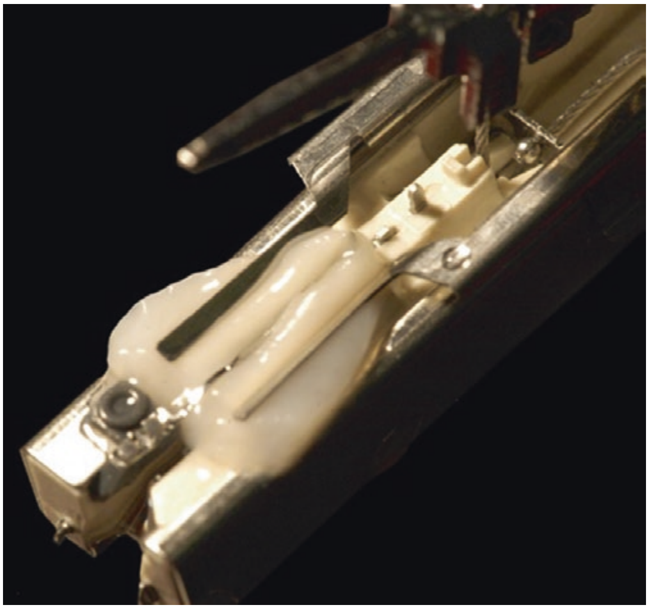

Fig. 23.10 Distal end of saphenous vein graft loaded into the C-Port xA distal anastomotic device. The edges of the vein graft are securely held by the clamps of the instrument, and the vein shield is deeply tucked into the graft, forming a hood. (*Courtesy of ©AESCULAP AG, Tuttlingen, Germany*)

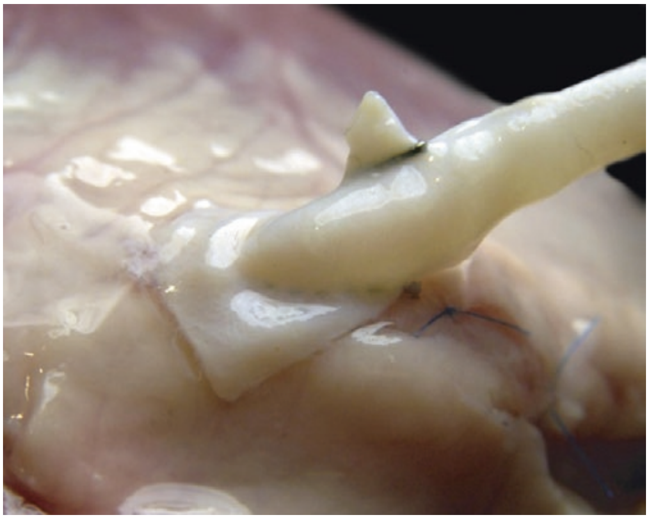

Fig. 23.11 Completed distal coronary anastomosis constructed by the C-Port xA device. The conduit is secured to the target vessel with multiple individual staples. The intimal components of the vein graft that had been physically handled and/or which were clamped by the device now lie outside the final staple line, and are thereby excluded from the actual anastomosis itself. (*Courtesy of ©AESCULAP AG, Tuttlingen, Germany*)

angiography was 92.1%, with a corresponding MACE rate of zero. Verberkmoes and associates randomized 71 patients to have their coronary grafts fashioned using either the C-Port xA system or using traditional hand-sewn techniques [33]. At 12 months follow-up, patency of target C-Port anastomoses, as evaluated by CT angiography, was 86.2%, not significantly different to that of the hand-sewn control group (87.5%).

Use of the C-Port system now extends beyond just saphenous vein to coronary anastomoses. Balkhy and colleagues constructed 25 internal mammary artery grafts in 24 patients using either the C-Port xA or Flex-A systems during OPCAB via sternotomy [34]. The same group has since integrated their use of the C-Port device into facilitating robotic-assisted totally endoscopic multi-vessel coronary revascularization on the beating heart [35]. The authors have used the Flex-A system to construct, endoscopically, and with robotic-assistance, anastomoses between the left and right internal mammary arteries, as well as grafts from each individual mammary artery to all major vascular territories of the heart. At a mean of 4 months follow-up, 85 grafts in 68 patients were evaluated by either CT or formal angiography, of which 80 were patent (94.1%).

The C-Port system has also been employed outside of the cardiac surgical arena; its use has been reported in both neurosurgery [36] and renal access surgery [37].

Others

Other distal coronary anastomotic devices include: nitinol U-Clips (Medtronic Inc., Minneapolis, MN), which are no longer clinically available in the United States, despite having been associated with promising results [38]; and the Trinity Clip, an iterative evolution of the Excimer laser-assisted non-occlusive anastomosis (ELANA) connector, which has demonstrated conceptual feasibility, but which is still being evaluated in animal models, and is not, at present, accessible in clinical practice [39–41].

Conclusions

Excellent long-term graft patency remains the primary goal of any surgical revascularization procedure, irrespective of how the operation itself is performed. Inter and intra-surgeon variability in surgical technique has the potential to significantly impact graft patency and, by consequence, clinical outcomes. Coronary anastomotic devices, both proximal and distal, can facilitate the construction of rapid, reproducible, compliant anastomoses, in potentially difficult-to-access areas, often via minimally-invasive incisions, with appreciable additional neuro-protective benefits under certain circumstances, thus mitigating some of the hazards inherent in manually constructing anastomoses in technically challenging or sub-optimal conditions. We routinely interrogate all of our off-pump coronary grafts intraoperatively using transit-time flow probes (Medistim USA Inc., Plymouth, MN), and, to date, in well over 4000 OPCAB procedures, we have not yet had to revise a graft that was constructed using either the Heartstring, PAS-Port or C-Port systems based on flow characteristics.

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24

Post-infarction Ventricular Septal Defect

Joseph Nader, Pierre Voisine, and Mario Sénéchal

High Yield Facts

- Post-infarction ventricular septal defect (VSD) is an early mechanical complication of acute myocardial infarction.
- It occurs in the myocardial territory of an occluded coronary artery.
- It can be isolated or associated with other complications such as free wall aneurysm or acute mitral regurgitation due to papillary muscle rupture.
- Cardiogenic shock, right ventricular dysfunction and emergent surgery are risk factors for higher operative mortality.
- Surgical treatment as a first-line approach to post-infarction VSD has traditionally been advocated.
- Delaying surgery (with or without preoperative mechanical support) and heart transplantation should be considered in selected clinical situations.

Epidemiology, Natural and Clinical History

Ventricular septal defects (VSDs) following acute myocardial infarction (AMI) remain an important concern, with a 30-day mortality rate approaching 100% with medical management alone [1]. The incidence of VSDs is relatively low in the current era, occurring in less than 0.5% of patients presenting with AMI. This low percentage is the direct consequence of the wider use of early thrombolytic therapies and more rapid access to percutaneous interventions in the acute medical management of AMI.

According to the GUSTO-I trial findings, almost all VSDs occur during the first day following AMI [2], with a median time of 16 h as reported in the SHOCK Trial [3]. The risk of death is highest in the early days following ventricular rupture, then gradually declines. This risk of early mortality is ranged between 19% and 54%, and maybe be directly influenced by some risk factors as cardiogenic shock with hemodynamic instability, early repair, right ventricular dysfunction, associated organ failure and complex VSDs [4]. These results are mainly reported in multicenter reports, as cited in Table 24.1 [1, 4–16].

The location of VSD is directly related to the culprit coronary artery at the source of the infarct and its vascularization of the interventricular septum. It is mainly anterior or apical in case of an anterior MI with an acute occlusion of the left anterior descending artery [17] but can be posterior in up to 50% of cases as a result of inferior MI due to the occlusion of a dominant right coronary artery or, in few cases, of an occluded dominant circumflex artery. In the latter case, acute mitral regurgitation may occur if the papillary muscle is located in the ischemic zone.

The result of this sudden septal rupture is a blood shunt from the left to the right ventricle, with increased pulmonary pressure that may lead to acute right ventricle dysfunction. A VSD should be suspected if a patient initially admitted for AMI, presents with sudden cardiogenic shock, persistent or recurrent chest pain, the new onset of a cardiac murmur, or a pulmonary congestion a few hours to several days after the initial event.

Transthoracic echocardiography (TTE) with Doppler evaluation is the recommended initial imaging modality if a VSD is suspected (Fig. 24.1). TTE confirms the presence as well as location and size of the defect and allows for the assessment of other complications such as valvular dysfunction, left ventricular wall motion abnormalities and right ventricle dysfunction, in the context of a left-to-right shunt. Further investigation with transesophageal echocardiography can be useful if TTE does not provide a thorough appreciation of these parameters. Patient should be kept in an appropriate intensive care unit with strict hemodynamic monitoring using a Swan-Ganz catheter and an arterial line. A coronary angiogram should be performed in the early hours after VSD diagnosis in order to promptly determine the optimal surgical strategy.

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Table 24.1 Risk factors and operative mortality in patients with surgical repair of post-infarction ventricular septal defect[a]

Author, date, journal	Patient group	Significant risk factors identified				Operative mortality
		Cardiogenic shock	RV dysfunction	Early repair	Posterior VSD	
Arnaoutakis et al. (2012), ATS	Database from the Society of Thoracic Surgeons (1999–2010), n = 2800	Yes	N/A	Yes	N/A	43% (n = 1235)
Cinq-Mars et al. (2016), IJC	Single-center cohort (1991–2014), n = 34	Yes	Yes	Yes	Yes	65% (n = 22)
Coskun et al. (2009), JCTS	Single-center cohort study (1990–2005), n = 41	Yes	N/A	Yes	Yes	34% (n = 14)
Cummings et al. (1989), ATS	Single-center cohort study, n = 42	Yes	Yes	Yes	Yes	42% (n = 14)
Dalrymple-Hay et al. (1998), STCVS	Single-center cohort study (1972–1995), n = 179	No	N/A	Yes	Yes	27% (n = 48)
Deja et al. (2000), EJCTS	Single-center cohort study (1986–1998), n = 117	Yes	No	Yes	No	35% (n = 35)
Hung et al. (2015), JCTS	Single-center cohort study (1995–2013), n = 47	No	N/A	Yes	N/A	36% (n = 17)
Killen et al. (1997), ATS	Single-center cohort study (1970–1994), n = 76	No	N/A	No	No	41% (n = 31)
Labrousse et al. (2002), EJCTS	Single-center cohort study (1971–2001), n = 85	Yes	Yes	N/A	No	42% (n = 36)
Moore et al. (1986), Circulation	Single-center cohort study (1979–1984), n = 25	Yes	Yes	Yes	Yes	56% (n = 14)
Pang et al. (2013), JCTS	Single-center cohort study (1999–2011), n = 38	Yes	Yes	Yes	No	40% (n = 15)
Parry et al. (1992), EHJ	Single-center cohort study (1980–1989), n = 108	Yes	N/A	Yes	No	47% (n = 38)
Rohn et al. (2013), Prague Medical Report	Single-center cohort study (2004–2012), n = 25	Yes	No	N/A	Yes	40% (n = 10)
Sibal et al. (2009), Heart, Lung and Circulation	Single-center cohort study (1992–2006), n = 36	Yes	Yes	Yes	Yes	53% (n = 19)

ATS Annals of Thoracic Surgery, *EHJ* European Heart Journal, *EJCTS* European Journal of Cardiothoracic Surgery, *IJC* International Journal of Cardiology, *JCTS* Journal of Cardiothoracic Surgery, *N/A* not available, *RV* right ventricle, *STCVS* Seminars in Thoracic and Cardiovascular Surgery, *VSD* ventricular septal defect

[a] Adapted from Cinq-Mars A, et al. Int J Cardiol 2016

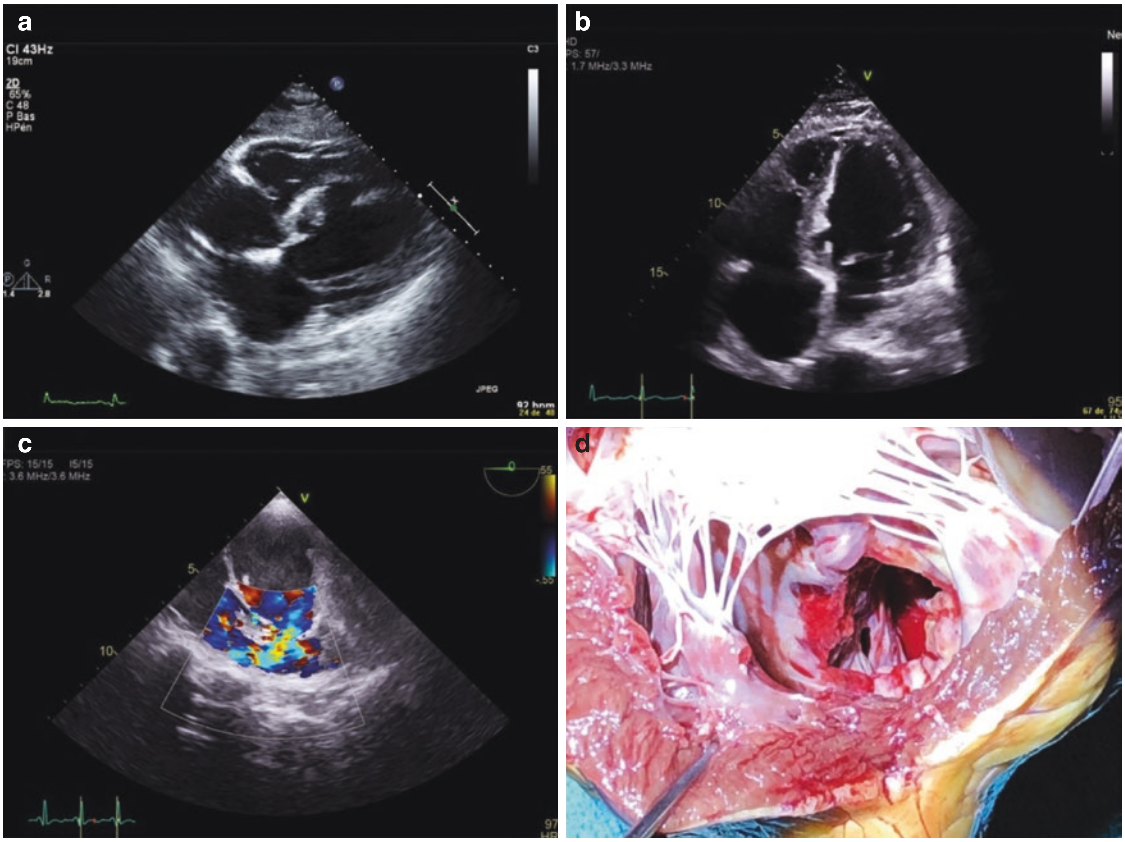

Fig. 24.1 (**a**, **b**) Transthoracic echocardiography showing the septal defect and the communication between right and left ventricle. (**c**) Transesophageal Echocardiography showing the Doppler colour flow between both ventricles. (**d**) Perioperative picture of the same VSD in (**a**–**c**), after harvesting the heart during heart transplantation procedure

Therapeutic Strategies and Options

Medical treatment with inotropic support and vasodilator agents can only temporarily alleviate symptoms and help to hemodynamically stabilize patients but cannot be considered curative. The septal defect must be closed in order to correct the left-to-right shunt and prevent the hemodynamic dysfunction related to right and left ventricle dyskinesis. Surgical treatment is thus the main approach to treat post-infarction VSD. Two main strategies are usually considered:

- *Emergent surgical closure of the defect*: In patients who are hemodynamically unstable, emergent surgery is sometimes required in the hours following the onset of cardiogenic shock. This involves a surgical repair of the defect in ischemic and friable ventricular tissue, a complex and difficult task that can be further complicated in case of recent thrombolytic therapy, associated with significantly increased perioperative bleeding risks.
- *Delayed VSD repair*: If the patient is stable and does not present signs of cardiogenic shock or valvular complications, the repair may be delayed by more than 1 week in order for the fibrotic myocardial tissue on the edges of the defect to replace friable, acutely infarcted myocardium. This bolsters the strength of the patch and reduces the risk of incomplete closure or recurrence.
- Delayed VSD repair can also be achieved in unstable patients through temporary mechanical assistance, with the same objective of performing surgery in fibrotic, more resistant myocardial tissue. An intra-aortic balloon-pump (IABP) [18] can be used to decrease left ventricular afterload and reduce the right-to-left shunt, but more invasive therapy with an extra corporeal membrane oxygenation (ECMO) or temporary percutaneously inserted mechanical assist devices (Impella® Recover LP 5.0, Abiomed Inc., USA; TandemHeart®, CardiacAssist Inc., Pittsburgh, PA) is often required [19–22]. These strategies allow for adequate delivery of oxygenated blood to peripheral organs and prevent multi-organ failure despite cardiogenic shock. Mechanical support can sometimes be used as a bridge to recovery in cases of small VSDs, or to stabilize patients eventually amenable to percutaneous closure of the defect with an Amplatzer® device. In most instances, however, surgical closure of the VSD is sought within 1–2 weeks of mechanical support. In some higher risk patients, for example those with a complex posterior VSD, mitral insufficiency and/or pseudoaneurysm formation, heart transplantation has also been suggested as a viable alternative (Table 24.2) [4, 23]. Heart transplantation could offer better long-term survival and quality of life, despite its inherent complications and limitations, for patients at particularly high-risk of presenting a residual VSD or severe left and/or right ventricular dysfunction despite optimal conventional surgical treatment.

Table 24.2 Indications of heart transplantation in post-infarction ventricular septal defect

Heart transplantation candidacy could be considered, when VSD is associated with:
• Extensive, severe, non-revascularizable coronary artery disease
• Persistent biventricular heart failure after an initial medical management of more than 1 week (inotropic support and/or ECMO)
• Massive initial AMI with a large VSD
• Presence of ischemic mitral regurgitation and/or pseudoaneurysm, associated with risk factors of poor surgical prognosis: – Posterior VSDs – Cardiogenic shock – RV dysfunction

AMI acute myocardial infarction, *ECMO* extracorporeal membrane oxygenation, *RV* right ventricle, *VSD* ventricular septal defect

The American Heart Association and European Society of Cardiology guidelines recommend an emergent surgical repair of the defect even in hemodynamically stable patients, in order to prevent the expansion of the rupture site or a rapid decrease in the clinical status [24, 25]. However, considering the higher mortality rate and risk of recurrence associated with early surgical repair, the actual trend is to delay surgery whenever possible.

Surgical Techniques

General Considerations

The appropriate surgical technique depends on the location of the septal defect. For that reason, an optimal morphological preoperative examination is necessary before surgery. Under general anesthesia and after median sternotomy, cardiopulmonary bypass is initiated with double caval venous drainage. Conduits can be harvested if concomitant coronary artery bypass grafting (CABG) is planned. As some coronary arteries may be severely stenosed or occluded the heart can be arrested with retrograde on top of antegrade cardioplegia for optimal myocardial protection. The defect is generally approached through the left ventricular free wall in the infarcted area or secondary aneurysm. Necrotic myocardial tissue may be completely debrided and replaced with a prosthetic patch, with minimally tension on myocardial wall, or only excluded by interposing a pericardial patch inside the heart cavity. The main goal of the surgical treatment is to restore a normal morphology and triangular shape of the left ventricle. Surgical sealants are frequently used on the ventriculotomy to prevent peri and postoperative bleeding.

Apical Septal Defect

In case of a distal apical defect, the cardiac apex is sliced until normal myocardial tissue is reached, completely excluding the ischemic tissue, unless the expected resection largely reduces the left and right ventricle volume. Once the defect is resected, both healthy free walls of right and left ventricle are primarily sewn together using a 0 polypropylene suture, including the septum between them, and the suture is reinforced with a PTFE or pericardial patch interposed from each side of the septum [26]. Ventriculotomy is closed using a first layer of interrupted sutures, doubled with a second layer of running sutures.

Small Ventricular Septal Defect

Direct repair of a small septal defect can be accomplished as described by Shumaker with a direct suture of the free septum to the free wall of the right ventricle using a pledgeted mattress sutures all around the rupture (Fig. 24.2a). In some cases, the defect may require a prosthetic patch on the apical septal portion (Fig. 24.2b). In some unstable patients with small defect (<15 mm of diameter), a percutaneous transcatheter closure using the Amplatzer® device, may be considered and seems to be more attractive than conventional surgery. It is used as a bridge to surgery in unstable patients, or even as a definitive treatment. The operative mortality varies widely and is assumed to be ranging from 14% to 66%, depending on the hemodynamic status of patients before the intervention. When it is used in stable patients, short- and long-term survival can be up to threefold-higher than in patients with cardiogenic shock [27–30].

Medium or Large Septal Defects

Open surgical treatment of these defects is the only viable therapeutic option. The larger width of the defect requires the use of a polyester or pericardial patch to replace the

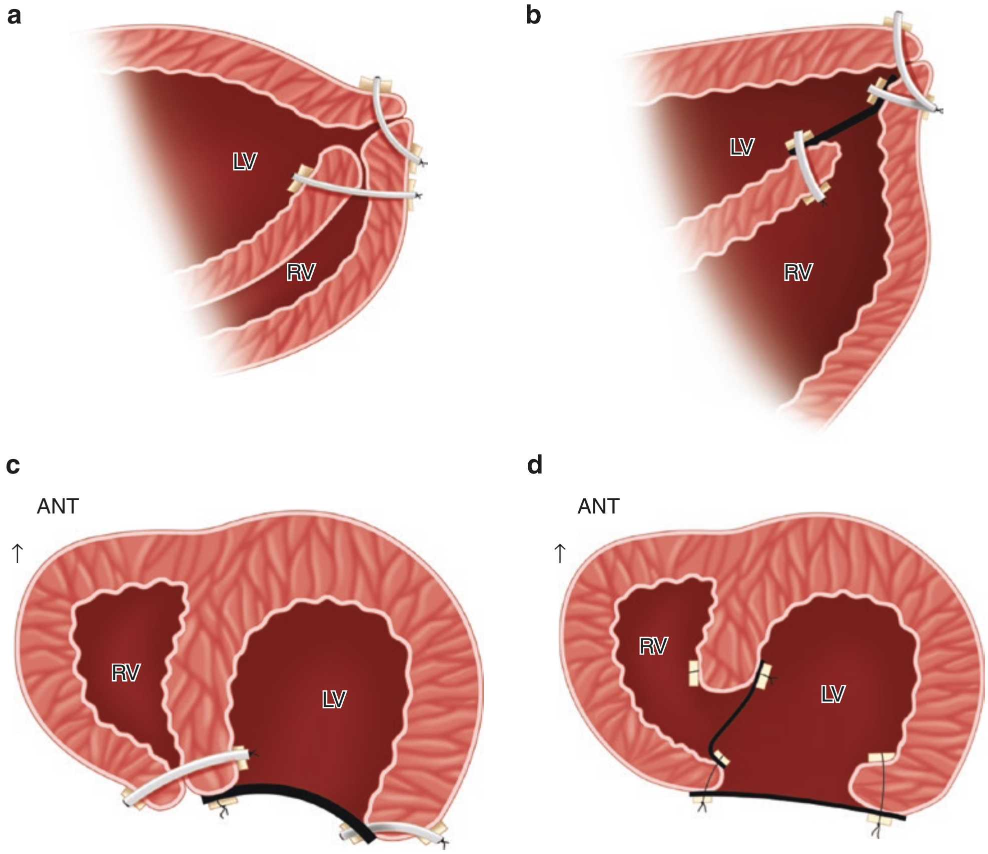

Fig. 24.2 Surgical repair of different patterns of post-MI VSD. (**a**) Small apical defect may be treated by sewing the free edge of the septal defect to the free wall of the right ventricle (RV) using an apical approach; if needed, an interposition of a prosthetic patch may be useful (**b**). In case of larger defect, a trans-left ventricular (LV) approach is indicated, and the septal defect may be directly repaired by sewing the free edge to the RV wall (**c**) or using a prosthetic patch (**d**). In both cases (**c**, **d**), the LV wall is closed using a prosthetic patch in the infarcted area

ruptured septum. The difficulty level of exposure and repair of the VSD is highly dependent on its location.

Anterior defects are often easier to expose and repair. The exclusion technique consists of sewing a larger polyester or pericardial patch on the septum. Using the trans-left ventricular approach, the septum is exposed, and the patch is sewn to the left ventricular endocardium adjacent to the infarcted area, in order to give a solid attachment to the sutures in normal myocardial tissue and prevent any enlargement of the preexisting defect. In this case, a 2-0 or 3-0 polypropylene suture with pledgets is used (Fig. 24.2c).

Posterior defects are harder to expose due to their location. Exposure requires a complete eversion of the heart, which increases the risk of laceration of the ischemic left ventricular wall. A triangular pericardial patch is directly sewn onto the mitral annulus using a 3-0 polypropylene suture, then to the septal portion of the defect and reflected to the left ventricular free wall with transmural pledgeted sutures as this free wall is located in the infarcted zone. The left ventricular wall is then closed using a PTFE or pericardial patch after resection of the necrotic tissues (Fig. 24.2d) [31, 32].

Concomitant Procedures

The surgical treatment of post-infarction VSD may require one or more concomitant procedures to treat other potential complications of MI.

In case of ischemic mitral regurgitation, a surgical intervention on mitral valve may be considered. The main mechanism of mitral regurgitation associated with VSD is papillary muscle necrosis and rupture. This complication is often treated by repairing the papillary muscle when it is possible; otherwise mitral valve replacement is preferred to mitral valve repair in ischemic mitral regurgitation, as it provides a more durable correction of mitral regurgitation [33]. Likewise, in post-infarction aneurysm, excision of the aneurismal sac is the first step in accessing the septal defect, and the free left ventricular wall repair is thus included in the global VSD repair procedure [34]. Finally, concomitant CABG may be required to treat the underlying coronary disease. Saphenous vein grafts can be used in emergent cases, but the use of the internal thoracic artery as a graft to the left anterior descending artery remains the gold-standard of CABG whenever possible. Concomitant CABG may increase the 30-day and long-term survival in patients presenting with VSD [35].

Postoperative Results and Prognosis

Post-infarction VSD remains a fatal complication in 30–40% of post-operative cases, while mortality reaches 100% with medical treatment alone. In recent years, improvements in the early management of AMI have led to a decrease in the incidence of post-infarction VSD as well as the mortality rate. Early thrombolysis of AMI and rapid coronary angioplasty and stenting are becoming widely used as first-line and emergent treatments of acute coronary syndromes with a resultant decrease in mechanical complications if AMI.

Nevertheless, risk factors associated with higher mortality following post-infarction VSD are well-recognized in the literature. These include:

- *Cardiogenic shock at presentation*: Initial cardiogenic shock, which mainly depends on the width of the infarcted area, is associated with an operative mortality ranging from 44% to 58% [6].
- *Inability to delay surgery*: The timing of surgery is crucial, as delayed surgery distances the patients from the early post-infarction inflammatory reaction and necrotic myocardial tissues. Repair in fibrotic tissue is more suitable and safer than in necrotic tissues.
- *VSD location*: Posterior VSDs carry a poorer prognosis than their anterior counterpart. Posterior VSDs are often a consequence of more complex AMI and more often present with concomitant mitral insufficiency. Moreover, surgical exposure of posterior VSDs is harder to accomplish [1].
- *Right ventricular dysfunction*: Right ventricular dysfunction remains a significant management challenge and is associated with higher operative mortality. It can be directly related to a right myocardial infarction, but more often the result of increased right ventricular volume and pressure afterload due to the acute left-to-right shunt.

Conclusion

Post-infarction VSD remains one of the most feared complications following AMI. The associated mortality is high and surgical closure remains the most appropriate treatment. The incidence of post-infarction VSD is decreasing nowadays, as a direct consequence of the early and improved management of AMI. We suggest herein an updated management algorithm (Fig. 24.3) for post-infarction VSD, according to the latest findings in the literature.

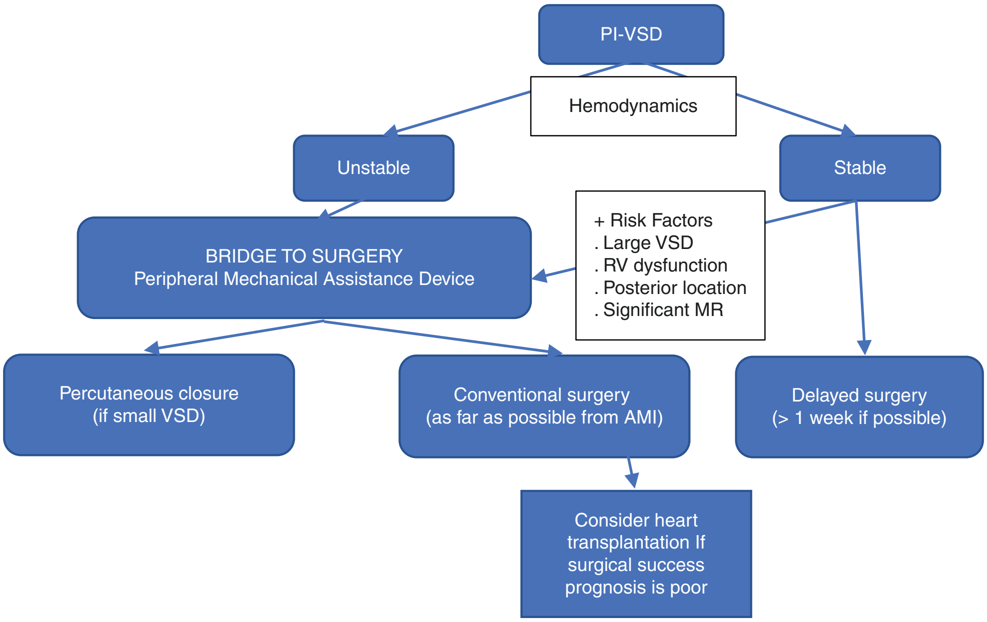

Fig. 24.3 Algorithm for therapeutic decision making in acute post-infarction ventricular septal defect. *MR* mitral regurgitation, *RV* right ventricle, *PI-VSD* post-infarction ventricular septal defect

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Ischemic Mitral Regurgitation

25

Michael Salna and Jack H. Boyd

High Yield Facts

- Ischemic mitral valve regurgitation (IMR) is a valvular consequence of ventricular pathology arising from chronic coronary artery disease.
- Surgical intervention is indicated in patients with severe IMR who remain symptomatic despite guideline-directed medical therapy.
- Trials comparing mitral valve repair to replacement in severe IMR identified no mortality difference but higher rates of reintervention among patients undergoing repair.
- Chordal sparing mitral valve replacement is recommended over repair in severe symptomatic IMR by the 2017 AHA/ACC guidelines, and by the AATS in those with basal aneurysms/dyskinesis, significant leaflet tethering, and/or severe left ventricular dilation.
- Randomized controlled trials have not demonstrated survival benefits for mitral valve repair in patients undergoing coronary artery bypass grafting with at least moderate IMR though several patient criteria support the inclusion of repair.
- Ongoing studies are investigating the use of stem-cell based therapies, percutaneous repair strategies, and transcatheter mitral valve replacement in IMR.

Epidemiology

Mitral valve regurgitation (MR) is the most common valvular heart disorder with an estimated five million people suffering from moderate or severe MR and rates increasing in an age-dependent manner [1]. One subtype, ischemic mitral regurgitation (IMR), is caused by pathologic left ventricular remodeling due to chronic coronary artery disease. This leads to Carpentier type I, II (acutely, from papillary muscle rupture), or IIIb dysfunction. More than 10% of patients with coronary disease develop at least moderate IMR [2] though, most commonly, clinically significant IMR (greater than moderate in severity) develops after myocardial infarction (MI). More than one million people in the United States are diagnosed with an MI each year, thereby contributing to the annual IMR burden each year [3].

Pathophysiology

As the ischemic left ventricle dilates, the mitral annulus dilates, and the papillary muscles are apically displaced, resulting in leaflet tethering and suboptimal coaptation (Fig. 25.1). Chronic regurgitation exacerbates this ventricular dilation, further worsening MR and leading to volume overload as a maladaptive process compensating for declining cardiac output. Patient prognosis worsens for each gradation of IMR severity, though this also tends to follow the severity of LV dysfunction [4].

Diagnosis and Assessment of Ischemic Mitral Regurgitation

Clinical examination is unreliable in MR as the classic systolic regurgitant murmur on auscultation may be absent due to a lower regurgitant volume from reduced LV contractility and high left atrial pressures. However, suspicion should be raised in a patient with known coronary artery disease who

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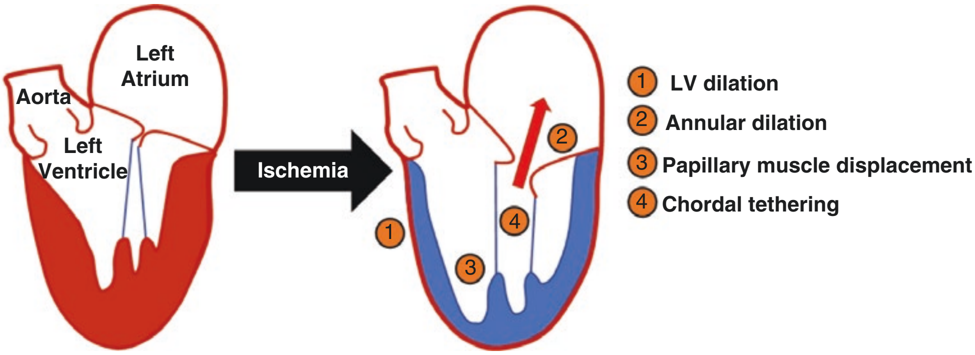

Fig. 25.1 Pathophysiology of ischemic mitral regurgitation

Table 25.1 Grading of chronic ischemic mitral regurgitation

Chronic mitral regurgitation severity			
Variable	Mild	Moderate	Severe
Effective regurgitant orifice (cm^2)	<0.2	0.20–0.39	≥0.4
Vena contracta (cm)	<0.3	0.3–0.6	≥0.7
Regurgitant volume (mL)	<30	30–59	≥60
Regurgitant fraction (%)	<30	30–49	≥50

IMR Caveats: ∗ERO may be underestimated by crescentic jet; RV may be lower with poor LV systolic function; VC may be underestimated by elliptical orifice shape

develops a new systolic murmur. Transthoracic echocardiography is essential to determine the valvular lesions, type of valvular dysfunction, and important characteristics such as regurgitant severity, LV size, functional abnormalities and secondary consequences such as pulmonary hypertension and left atrial enlargement. Classic features of ischemic MR include posterior wall remodeling causing apical displacement of the posterolateral papillary muscle. This tethers the posterior leaflet, usually at P2 and P3, deforms the anterior leaflet, and subsequently displaces the MV coaptation point posteriorly creating a relative anterior leaflet prolapse and a posteriorly directed MR jet.

The AHA/ACC acknowledges the optimal criteria for defining the severity of IMR are controversial. Echocardiographers may underestimate MR severity using Doppler to calculate effective regurgitant orifice area (ERO) by flow convergence because of the crescentic shape of the regurgitant jet [5]. The 2017 AHA/ACC guidelines define severe secondary MR as an effective regurgitant orifice area of ≥0.40 cm^2 (with the caveat that an ERO cutoff >0.2 cm^2 is more sensitive), a regurgitant volume of ≥60 mL, or a regurgitant fraction of ≥50% (Table 25.1) [6]. However, some data suggest that adverse outcomes are associated with smaller EROs in IMR given that smaller regurgitant volumes may represent a large fraction of regurgitation in the presence of poor ventricular systolic function.

Amongst this lack of definitive criteria, what can be agreed upon is that an integrated approach incorporating multiple echocardiographic and clinical variables should be used to grade IMR and consequently determine the appropriateness of surgical intervention.

Medical Therapy

Medical therapy for IMR is predominantly based on guideline-directed heart failure management and should include an angiotensin-converting enzyme (ACE) inhibitor and a beta blocker, both independent predictors of improved survival in patients with LV dysfunction [7]. Afterload-reducing agents such as ACE-inhibitors may decrease regurgitant volume by lessening resistance to forward flow. The primary goal of these agents is to reverse remodel the LV, thereby ameliorating papillary muscle tethering and consequently reducing the severity of IMR. Diuretics can also be added in the presence of fluid overload.

Cardiac resynchronization therapy (CRT) with biventricular pacemaker is another well-established therapy for NYHA III-IV patients with reduced LV ejection fraction, QRS > 120 ms, and chronic severe secondary MR, though not necessarily IMR specifically. This modality improves, but does not eliminate, MR through decreasing left ventricular end-systolic volume, increasing closing forces, and resynchronizing papillary muscle contraction [8]. Notably, withdrawal of CRT has been shown to cause recurrence of MR [9].

Indications for Surgical Intervention

The 2016 AATS Consensus Guidelines for IMR recommend surgical intervention in patients with severe IMR who remain symptomatic despite the guideline directed medical and cardiac device therapy referenced earlier [10].

The question then becomes, how should the mitral valve best be addressed? There is significant debate regarding whether mitral valve replacement (MVrpl) or mitral valve repair (MVrpr) is the optimal management strategy for patients with severe IMR. The two-year outcomes of the 2016 Cardio-Thoracic Surgery Network (CTSN) trial, a randomized multicenter trial randomizing 251 patients with severe IMR to either MVrpl or MVrep, found no significant difference in survival or left ventricular reverse remodeling. However, there was significantly higher recurrence of moderate to severe MR in the repair group over the replacement group (58.8% vs. 3.8%, $p < 0.001$), resulting in more heart-failure related admissions and adverse events.

Factors found to predict a higher likelihood of a successful and durable repair are divided into echocardiographic measures of leaflet tethering and the degree of LV remodeling. The most widely published preoperative echocardiographic predictor of MR recurrence after MVrpr is an angle between the tip of the anterior leaflet and the plane of the annulus greater than 30–45° [11, 12]. The CTSN investigators identified basal aneurysm/dyskinesis as the strongest predictor of recurrent IMR, likely due to its reflection of severe LV ischemic remodeling with associated leaflet tethering and annular dilation [13].

The updated 2017 AHA/ACC Valvular Disease Guidelines recommend consideration of chordal sparing MVrpl over repair in those with severe symptomatic IMR [6]. The AATS recommends MVrpl in those patients who have **basal aneurysm/dyskinesis, significant leaflet tethering, and/or severe LV dilation (end diastolic dimension > 6.5)**, and MVrpr if these features are absent and the likelihood of successful repair is high, based on surgeon expertise and anatomy.

Mitral Valve Replacement

While the technical steps of mitral valve replacement will be discussed elsewhere in this book, several principles and suggestions to consider are:

1. Preservation of the subvalvular apparatus—excision will distort ventricular geometry and impair LV function
2. Avoidance of left ventricular outflow tract obstruction—we recommend a triangular resection of A2 and slit incision of P2 to avoid post-operative obstruction
3. Suture placement—pay particular attention to the anterolateral commissure and the posterior annulus where the noncoronary cusp of the aortic valve and circumflex artery are at risk, respectively
4. Bioprosthetic vs. mechanical valve—considerations include durability, the need for permanent anticoagulation, and patient preference. Recent literature suggests that mechanical prostheses have a long-term mortality benefit compared with biologic prosthesis until age 70 in the mitral position [14].

Mitral Valve Repair

The primary goal of mitral valve repair is to address the underlying valvular pathology in order to achieve a competent valve without disrupting normal ventricular function.

As LV dilation is one of the most common etiologies of IMR, most cases involve annular dilation and thereby benefit from restrictive ring annuloplasty. Though the posterior annulus is the most commonly dilated segment, the AATS recommends complete (rather than incomplete) annuloplasty rings contoured to the shape of the native, healthy mitral valve, as these more reliably prevent adverse annular remodeling after repair [10]. However, an isolated restrictive annuloplasty ring does not address the underlying problem in IMR—leaflet tethering from ischemia-induced LV wall distortion. Additional mitral valve and subvalvular repair strategies such as papillary muscle slings and chordal cutting will be described later in this book.

Several, less commonly used, approaches to repairing IMR target specific mechanisms of regurgitation. External restraint devices such as the Corcap (Acorn Cardiovascular Inc., MN) have been shown to have long-term beneficial effects at 5-years on LV reverse remodeling by restraining ventricular dilation thereby attempting to reposition the papillary muscles to their original locations [15]. Another restraint device, the Coapsys (Myocor, Inc., Maple Grove, MN), aims to reshape the ventricle and compress the mitral annulus, thereby repositioning the papillary muscles via inward tension on a PTFE-coated subvalvular transventricular chord anchored by anterior and posterior epicardial pads [16]. While these devices had promising results, their integration into mainstream operating rooms has not yet materialized.

Concomitant Coronary Bypass Grafting

As the primary cause of IMR is ischemia induced LV dilation, surgical revascularization of ischemic territories may improve LV function and reduce LV dilation, thereby restoring mitral annular geometry and the function of the subvalvular apparatus. There have been several randomized-control trials examining the incremental benefit of performing MVrpr with restrictive annuloplasty in addition to coronary revascularization in patients with moderate IMR (Table 25.2).

The 2017 AHA/ACC guidelines state that MV surgery is reasonable for those with chronic severe IMR undergoing CABG though question the utility of MVrpr in those with chronic moderate IMR. Conversely, the 2016 AATS consensus guidelines state that the inclusion of MVrpr during CABG is up to the heart team and surgeon caring for the patient. Criteria that may be used to support the inclusion of MVrpr include:

- Elevated left sided pressures and dyspnea
- Experienced surgical team whereby the incremental risks of including MVrpr are low

- Younger and healthier patients
- Infarcted or aneurysmal posterolateral left ventricular wall
- No suitable coronary targets in ischemic regions
- Annular dilation exceeding 38–40 mm
- Significant left atrial enlargement

Percutaneous Therapy

The percutaneous treatments of mitral regurgitation are promising alternatives for IMR patients who are poor surgical candidates and are refractory to guideline directed medical therapy. As it is still not known who will benefit from MV surgery for IMR, the development of novel minimally invasive strategies addressing common IMR mechanisms may open the door to new hybrid strategies in treating coronary disease with IMR.

Leaflet Apposition Therapy (MitraClip)

The MitraClip device (Abbot Vascular, CA) is the most widely used transcatheter MVrpr technique. The device deploys a clip which cinches the anterior and posterior leaflets together at the location of the regurgitant jet, creating a double orifice MV (Fig. 25.2). While MitraClip implantation can improve hemodynamics, this therapy predominantly targets symptoms as the underlying mechanism of IMR—either leaflet tethering or annular dilation, is not addressed.

The MitraClip is not yet approved for IMR in the US though there are ongoing randomized trials including the COAPT and MITRA-FR trials. The largest completed trial to date, EVEREST II, demonstrated comparable survival with conventional MV surgery at 5-years though significantly higher rates of recurrent moderate to severe MR (12% vs. 2%, $p = 0.02$) and the need for surgical reintervention (28% vs. 9%, $p = 0.003$) in the MitraClip group [17]. European and American registry data demonstrated >90% initial success rates though >20% rehospitalization rates due to heart failure symptoms within 1-year [18, 19] except in one trial which demonstrated no difference [20]. The current 2017 EACTS valve guidelines recommend Heart Teams consider percutaneous edge-to-edge repair for non-operative patients with LVEF <30% who have refractory symptoms despite optimal medical or cardiac resynchronization therapy [21].

Table 25.2 Randomized controlled trials examining the incremental benefit of concomitant mitral valve repair and coronary revascularization in patients with moderate IMR

Trial	Comparisons	Outcomes
POINT (2009)	CABG (n = 54) vs. CABG + MVrpr (n = 48)	• No difference in 5-year survival (underpowered for significance) • MVrpr + CABG → significant improvement in NYHA class, LVEF, and MR grade
RIME (2012)	CABG (n = 39) vs. CABG + MVrpr (n = 34)	• No difference in 1-year survival • CABG + MVrpr → improved peak O_2 consumption (primary end point), LV reverse remodeling, NYHA class, and MR severity
CTS Network (2016)	CABG (n = 151) vs. CABG + MVrpr (n = 150)	At 2 years: • No difference in survival or LV reverse remodeling • Higher rate of moderate or severe recurrent MR in CABG alone group (32.3% vs. 11%, $p < 0.001$) • No difference in quality of life, adverse events, or readmissions

CABG coronary artery bypass grafting, *IMR* ischemic mitral regurgitation, *LVEF* left ventricular ejection fraction, *MR* mitral regurgitation, *MVrpr* mitral valve repair, *NYHA* New York Heart Association

Therapies to Address Annular Dilation (Carillon, Cardioband, Mitralign)

The Carillon Mitral Contour System (Cardiac Dimension Inc., WA) is an indirect annuloplasty system implanted in the coronary sinus around the mitral annulus and reduces MR by compressing the posterior mitral annulus in the septal-lateral dimension. Several small studies have demonstrated possible efficacy of this device in patients with IMR and it is currently being investigated in randomized multicenter trials [22, 23].

The Cardioband (Edwards, CA) is a direct transcatheter annuloplasty system which anchors to several points along the posterior annulus under 3D echocardiographic guidance [24]. After implantation, the system is contracted to narrow the septal-lateral dimension of the MV annulus until the MR is reduced.

Finally, the Mitralign (Mitralign, MA) system uses tissue plication to reduce annular dimensions by inserting pledgeted sutures into the posterior and anterior commisures and cinching them to reduce the annulus [25]. Both the Cardioband and the Mitralign have demonstrated sustained short-term reductions in high-risk patients with secondary MR.

Transcatheter Mitral Valve Replacement

One of the primary disadvantages of transcatheter repair techniques is the inability to target all anatomic variations of MR. While transcatheter MVrpl offers a more universal solution to MR, regardless of mechanism, the nonrigid mitral annulus, large variation in annular sizes, and saddle-shaped geometry of the MV pose unique challenges for this therapy.

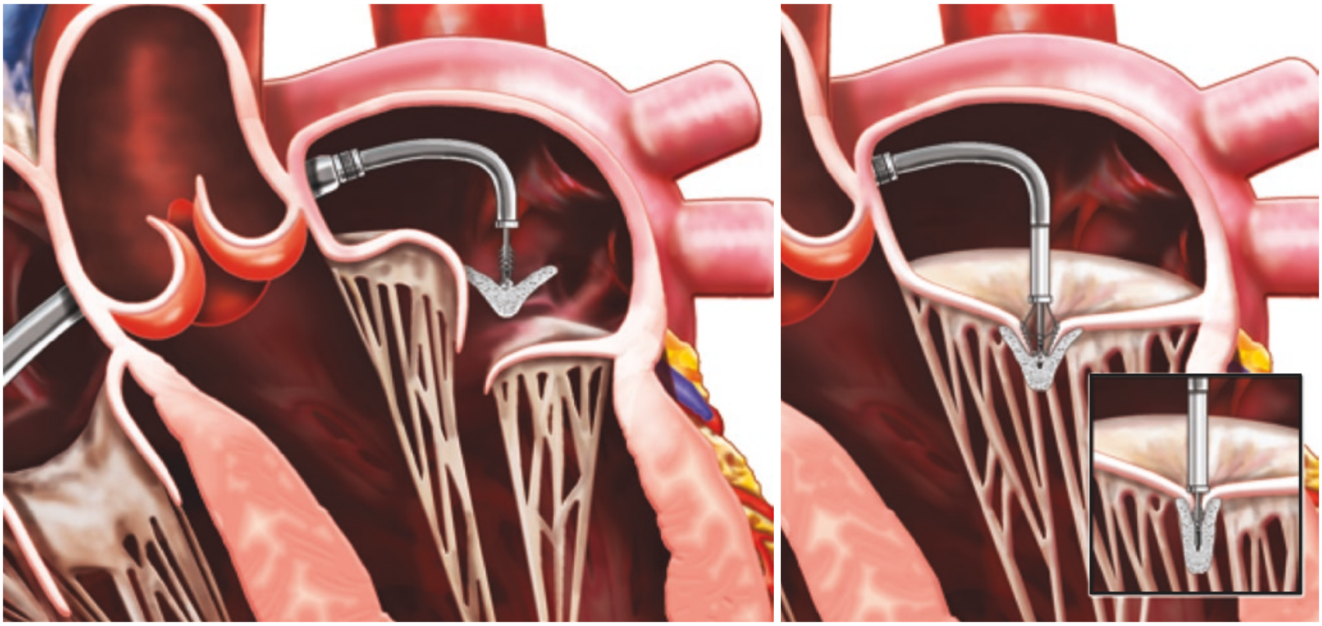

Fig. 25.2 The MitraClip device (Abbot Vascular, CA). (Adapted from Feldman, T and Young A. "Percutaneous Approaches to Valve Repair for Mitral Regurgitation." JACC 2014; 63(20): 2057–68)

While devices are still being trialed, two-year follow-up data with the transcatheter FORTIS mitral valve (Edwards, CA) had 54% mortality (with 5 of the 13 enrolled non-operative patients dying within 30 days of the procedure) though demonstrated no recurrence of MR in the remaining patients [26]. The Intrepid TMVR (Medtronic, MN) is being tested in the APOLLO trial. The early data appears promising with successful implantation in 48 of 50 high risk surgical patients. There is 14% 30-day mortality and dramatic reductions in NYHA class at most recent follow-up [27]. Transcatheter MVrpl has been also successfully performed in a valve-in-valve fashion with transcatheter valves developed for the aortic position in failed bioprosthetic valves and failed annuloplasty rings in patients deemed high risk for reoperation [28]. There are currently many more TMVR systems being evaluated at this time with multiple ongoing trials currently assessing their use in patients with severe MR who are at high or prohibitive surgical risk.

Future Directions

IMR is challenging to treat because it is simply a valvular symptom of a ventricular pathology. While there is no agreement yet on the optimal strategies to address the mitral valve itself, CABG and stenting are currently the only interventional therapies which directly addresses ischemia-induced ventricular remodeling. Autologous stem-cell based treatments are being trialed to reverse remodel ischemic myocardium post-myocardial infarction [29]. Bone marrow-derived endothelial progenitors have been found to promote neovascularization and reductions in infarct size though randomized multicenter trials, such as CONCERT-HF, DREAM HF-1, and BAMI, are ongoing to determine whether there are meaningful impacts on patient outcomes [30, 31].

As the fields of cardiology and cardiac surgery continue to integrate, the role of the heart team will become increasingly more relevant in IMR—with the prospect of hybrid strategies being more commonly employed such as open coronary bypass and transcatheter mitral interventions or percutaneous coronary interventions with surgical valve interventions.

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Post-infarction Ventricular Aneurysms

26

Manish K. Soni and Shahzad G. Raja

High Yield Facts

- True aneurysms are sequelae of transmural myocardial infarction.
- True aneurysms have a broad-based neck in relation to the rest of the aneurysm with a wall containing all three layers of cardiac tissue.
- False aneurysms or pseudoaneurysms are rare complications of myocardial infarction and represent a contained myocardial rupture.
- The base of the pseudoaneurysm typically comprises a narrow neck opening into a saccular area with a wall devoid of endocardial or myocardial elements.
- In 90% of cases, the left ventricular aneurysm is located at the apex of the heart or in the anterior wall, and in 10%, it is in the posterior-inferior wall.
- Majority of the pseudoaneurysms are located on the posterior, lateral, apical or inferior surface of the left ventricle and not on the anterior surface.
- Generally patients with true or false aneurysm may present with nonspecific complaints of chest pain, dyspnea, or even be asymptomatic.
- Left ventriculography has been the gold standard modality to distinguish pseudoaneurysm from true left ventricular aneurysm with a diagnostic accuracy of >85%.
- Once the diagnosis of pseudoaneurysm is established, surgical correction is usually mandatory.
- The presence of true left ventricular aneurysm alone is not a surgical indication. Surgery in case of true aneurysm is indicated when concomitant, persistent angina, refractory heart failure, thromboembolism, or life-threatening tachyarrhythmias occur.
- Endoventricular circular patch plasty is the preferred surgical option for treating true left ventricular aneurysms.

Introduction

Aneurysms of the left ventricle are of two types: true and false (or "pseudo") (Fig. 26.1). True aneurysms are sequelae of transmural myocardial infarction. They vary widely in size

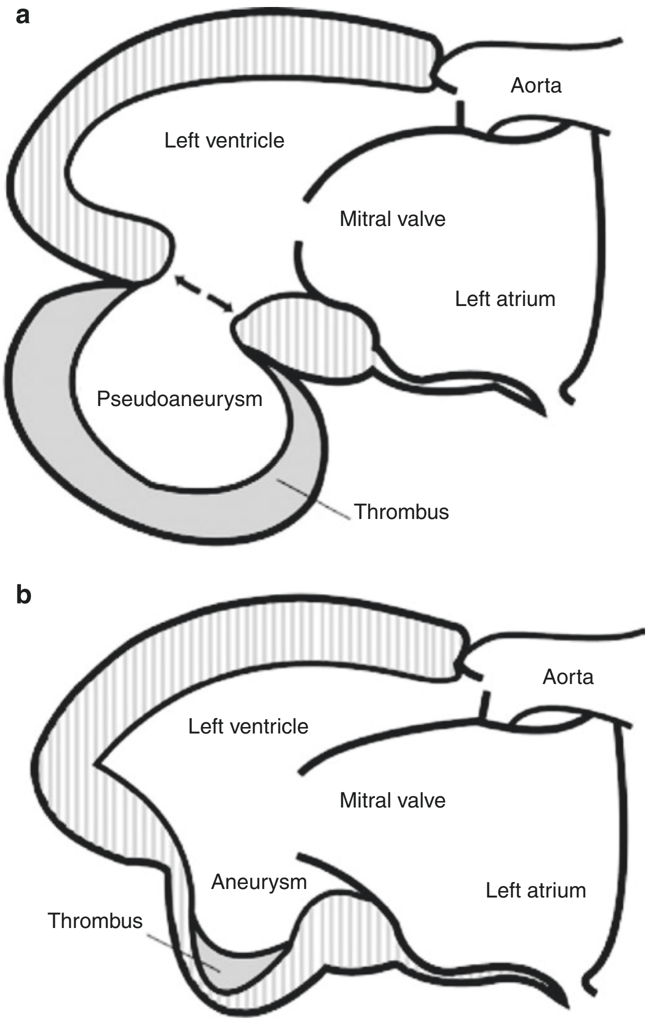

Fig. 26.1 (**a**) Left ventricular pseudoaneurysm. (**b**) Left ventricular aneurysm

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Table 26.1 Causes of left ventricular pseudoaneurysms

Myocardial infarction
Inferior
Anterior
Surgery
Mitral valve replacement
Aneurysmectomy
Aortic valve replacement
Mitral valvotomy
Aortic valvotomy
Trauma
Penetrating
Blunt
Infection
Abscess
Endocarditis

Table 26.2 Comparison of true and false left ventricular aneurysms

Feature	True aneurysm	False aneurysm
Histology	Contains all three layers of cardiac tissue	Lined by pericardium and mural thrombus
Pathogenesis	Maladaptive post-infarction ventricular remodeling	Ventricular rupture and containment by pericardial adhesions
Location	90% apical or anterior	90% inferior or posterior
Echocardiography	Ratio of the maximal internal neck width (O_{max}) to the maximal parallel internal diameter of the aneurysm (D_{max}) between 0.9 and 1.0	Ratio of the maximal internal neck width (O_{max}) to the maximal parallel internal diameter of the aneurysm (D_{max}) <0.5
Complications	Congestive heart failure, embolic events, ventricular arrhythmias	Congestive heart failure, embolic events, ventricular arrhythmias, tamponade
Treatment	Medical therapy or surgery	Surgery

and compliance, infrequently undergo progressive expansion, and seldom rupture. True aneurysms represent the extreme of maladaptive post-infarction remodeling and develop as a consequence of wall thinning. They characteristically have a broad-based neck in relation to the rest of the aneurysm with a wall containing all three layers of cardiac tissue [1].

False aneurysms or pseudoaneurysms are rare complications of myocardial infarction and represent a contained myocardial rupture. A pseudoaneurysm does not contain all the three layers of the myocardium and is frequently lined by pericardium and mural thrombus [2, 3]. The base of the pseudoaneurysm typically comprises a narrow neck opening into a saccular area with a wall devoid of endocardial or myocardial elements [4]. Pseudoaneurysms are most often a consequence of myocardial infarction but can also result from surgery, trauma, myocardial dysplasia, and infection [5] (Table 26.1). In contrast to true left ventricular aneurysms, false aneurysms have a tendency to rupture and, therefore, require expeditious operative management soon after the diagnosis is made, even in asymptomatic patients [6] (Table 26.2).

Incidence

True left ventricular aneurysms occur in approximately 7.6% of patients with coronary artery disease, most commonly as a complication of myocardial infarction [7]. On the other hand, rupture of the free wall of the left ventricle is a catastrophic complication occurring in 4% of patients after myocardial infarction and in 23% of those who die of myocardial infarction [8]. The survival rates of patients with chronic true left ventricular aneurysms are similar to those of patients without aneurysms after adjustment is made for the degree of left ventricular dysfunction and functional impairment. In contrast, patients with pseudoaneurysms have a high risk of spontaneous rupture and death if managed without surgical intervention [1].

Pathophysiology

Inferior myocardial infarctions account for approximately twice as many cases of pseudoaneurysms as anterior myocardial infarctions. The predilection for inferior myocardial infarction to result in left ventricular pseudoaneurysm is consistent with the location of pseudoaneurysms on the posterior, lateral, apical or inferior surface of the left ventricle and not on the anterior surface [9].

In contrast to left ventricular pseudoaneurysms, only about 4% of true left ventricular aneurysms are located at the posterolateral or diaphragmatic surface [10]. One proposed explanation for the relative lack of anterior left ventricular pseudoaneurysms is that anterior rupture may be more likely to result in hemopericardium and death than posterior rupture [11]. Because hospitalized patients usually are in the recumbent position, an inflammatory reaction of the posterior pericardium may result in pericardial adhesions and the formation of a posterior left ventricular pseudoaneurysm rather than cardiac tamponade.

The diameter of a left ventricular aneurysm is typically from 1 to 8 cm. In 90% of cases, the left ventricular aneurysm is located at the apex of the heart or in the anterior wall, and in 10%, it is in the posterior-inferior wall [12, 13]. The pericardium generally adheres to the wall of the aneurysm.

In experimental studies of dogs with transmural myocardial infarction but without collateral circulation [14], the interruption of blood flow caused almost immediate cessation of contractile activity. Myocyte death started within 20 min. Within a few days, the endocardial surface of the developing left ventricular aneurysm became smooth and thin, with fibrin deposition, thrombus formation, and loss of trabeculae in at least 50% of dogs. Inflammatory cells migrated into the infarct zone 2–3 days later and contributed to lysis of the necrotic myocytes approximately 5–10 days after the myocardial infarction, at which point rupture of the myocardial wall occurred in some dogs. Left ventricular rupture was relatively uncommon after the aneurysmal ventricular wall was replaced with fibrous tissue.

Clinically, the effect of increased tension in the involved myocardial wall leads to the wall's progressive thinning and protrusion [15]. This phenomenon is explained by Laplace's law ($\sigma = Pr/2h$), which states that, at a constant ventricular pressure (P), an increased radius (r) of curvature and a decreased wall thickness (h) of the affected portion of the heart contribute to increasing tension (σ) of the myocardial muscle fibers and promote the deformation and expansion of the ischemic ventricular wall. Functionally, such alteration involves loss of the ventricle's original shape, causing volume overload in end-diastole [16]. Volume overload leads to compensatory hypertrophy in the adjacent viable myocardium, thus increasing oxygen consumption. Approximately 2–4 weeks after myocardial infarction, vascularized granulation tissue appears, which is then replaced 6–8 weeks later by fibrous tissue, resulting in the formation of a chronic aneurysm [13].

Transmural necrosis, which leads to the formation of a left ventricular aneurysm, involves two main phases: early expansion and subsequent remodeling. The early expansion occurs in the area of the myocardial infarction, whereas the remodeling phase affects the muscle fiber cells, leading to fibrosis and changes in the geometry of the ventricular cavity [17]. These changes result in progressive ventricular dilation, increased wall tension, and altered systolic function, leading to irreversible contractile dysfunction.

Clinical Features

Generally patients with true or false aneurysm may present with nonspecific complaints of chest pain, dyspnea, or even be asymptomatic. In a published case series of 290 patients with pseudoaneurysms, 36% of patients presented with heart failure, 30% with chest pain, and 25% with dyspnea. Over 10% of the aneurysms were diagnosed incidentally by various imaging techniques [5]. In another study including 52 patients with pseudoaneurysms, 25 patients were asymptomatic at the time of diagnosis with the remainder having a constellation of nonspecific symptoms similar to the prior study [18]. Less commonly, patients with either pseudoaneurysms or true aneurysms can present with arrhythmia or systemic embolization [9]. Physical examination findings are also nonspecific and may include a displaced and dyskinetic point of maximal impulse, signs of heart failure, and in the case of pseudoaneurysm, a to-and-fro murmur [5].

Angina, the most prevalent symptom of left ventricular aneurysm, has been attributed to volume overload in the left ventricle and a resultant increase in oxygen consumption [19]. Any functional mitral regurgitation can exacerbate ventricular overload, progressively leading to the onset of heart failure. Dyspnea, the second most frequent symptom, occurs because of a combination of systolic and diastolic dysfunction. In more than one third of patients, atrial or ventricular arrhythmias cause palpitations, syncope, or sudden death, or they exacerbate angina and dyspnea [19].

Investigations

Electrocardiogram

Persistent ST segment elevation, Q waves, or nonspecific ST abnormality may be present on the electrocardiogram but are not sensitive or specific for either of these entities [20].

Chest X-Ray

The most common chest X-ray finding in these patients is an enlarged cardiac silhouette, although a discrete bulge on the cardiac border has been described in patients with pseudoaneurysms [21] (Fig. 26.2).

Echocardiography

Transthoracic echocardiography (TTE) is the most common modality to diagnose left ventricular aneurysms. However, the distinction between pseudoaneurysm and true aneurysm proves challenging with TTE [9]. In an analysis of five patients with pseudoaneurysm diagnosed by TTE, echocardiographic characteristics most suggestive of pseudoaneurysm included a sharp discontinuity of the endocardial border at the base of the pseudoaneurysm, a saccular or

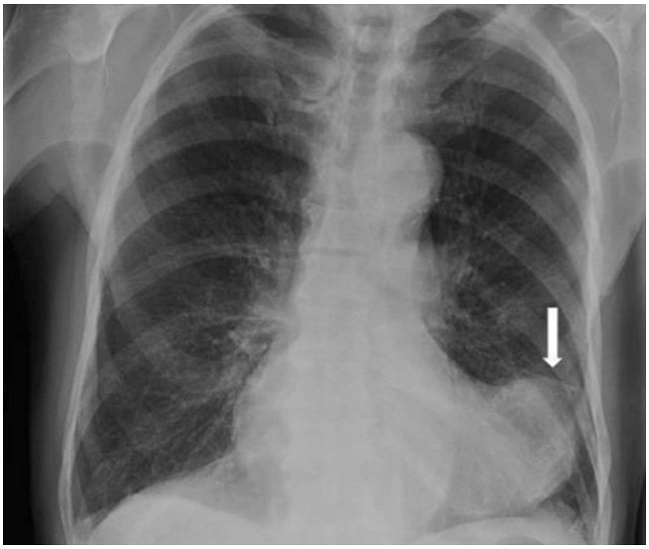

Fig. 26.2 Chest-X ray showing bulge (white arrow) along the left cardiac border in a patient with pseudoaneurysm

globular contour of the aneurysm, and a narrow orifice compared with the aneurysm fundus diameter [22]. In another TTE-based study, similar parameters were identified to support the diagnosis of pseudoaneurysm. The ratio of the maximal internal neck width (O_{max}) to the maximal parallel internal diameter of the aneurysm (D_{max}) was <0.5 in pseudoaneurysms with a ratio between 0.9 and 1.0 in true aneurysms [23]. However, a subsequent report demonstrated suboptimal specificity of this criterion [5]. Color flow Doppler has been used to detect turbulent flow through the neck of the pseudoaneurysm, but the absence of such flow does not confirm a true aneurysm, making this finding specific but not sensitive [20].

Left Ventriculography

Left ventriculography has been the gold standard modality to distinguish pseudoaneurysm from true left ventricular aneurysm (Fig. 26.3) with a diagnostic accuracy of >85%. The most useful combination of findings to confirm pseudoaneurysm includes a narrow orifice leading into a saccular aneurysm [18] (Fig. 26.4). This diagnostic investigation is performed in conjunction with selective coronary angiography to determine the extent of coronary disease. Projections of the mobile blood pool that do not show the wall may lead one to fail to distinguish some false aneurysms from some true aneurysms. A false aneurysm might be missed entirely if it is filled with thrombus. Although uncommon, the potentially high load of iodinated contrast agent may cause renal failure, especially in patients with diabetes. Therefore, noninvasive imaging is often performed in place of ventriculography.

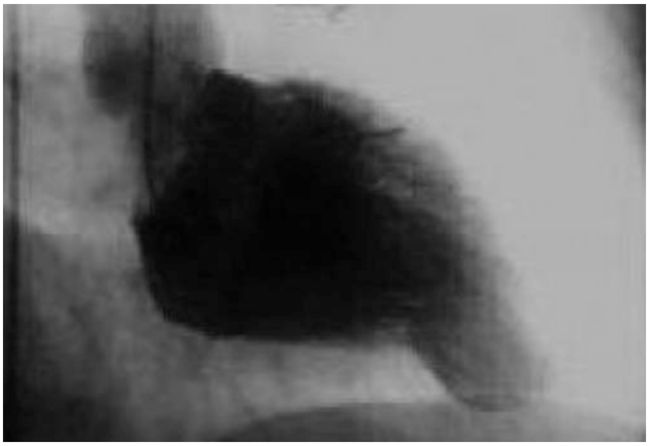

Fig. 26.3 Left ventricular (LV) cineangiogram obtained during diastole depicts a large true aneurysm involving the anterior and apical walls of the LV

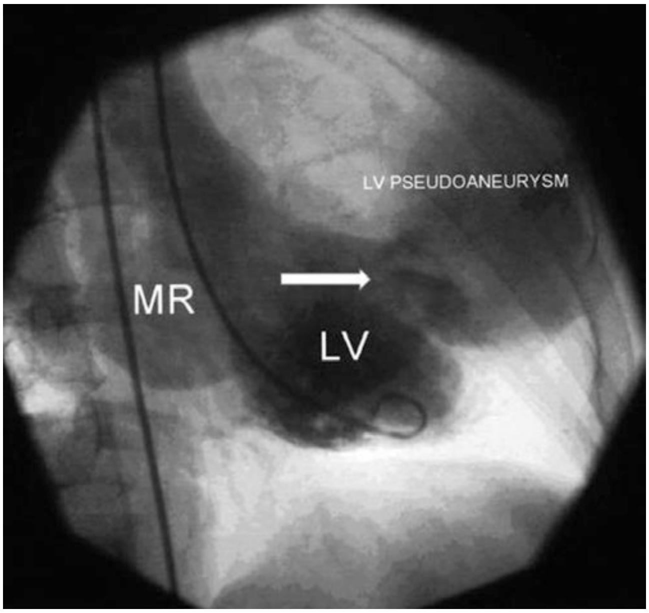

Fig. 26.4 A left ventriculogram in the right anterior oblique view shows a large left ventricular pseudoaneurysm arising from the lateral wall of the left ventricle (LV) and grade 2 mitral regurgitation (MR). The white arrow points to the narrow orifice leading into a saccular aneurysm

Computed Tomography

Computed tomography (CT) scanning is a reliable and noninvasive modality for identifying left ventricular aneurysms and for assessing resectability. After a myocardial infarction occurs, CT may be used to demonstrate regional wall thinning, as well as the complications of infarction, such as left ventricular aneurysm and mural thrombus. In patients with ischemic heart disease, electron-beam CT (EBCT) may be used to assess left ventricular segmental dysfunction; in these patients, EBCT demonstrates reductions in wall thickening and in wall motion. EBCT has also been used to monitor LV remodeling after acute myocardial infarction. Multidetector-row CT (MDCT) (i.e., CT in which 16–64 detectors are employed simultaneously) has now replaced EBCT [24].

CT is as accurate as two-dimensional (2-D) echocardiography.

For patients with ventricular aneurysms, CT is fast and provides clear resolution of the left ventricle; CT provides improved localization and more accurate estimation of the extent of wall thinning after infarction, as compared with projectional techniques, such as left ventriculography, and with most scintigraphic techniques. However, the iodine-based contrast material may cause renal failure, and the radiographic exposure is greater with MDCT than with cardiac catheterization (e.g., 13 Sv).

The site and extent of anterior and posterior aneurysms of the left ventricle may be well demonstrated with CT

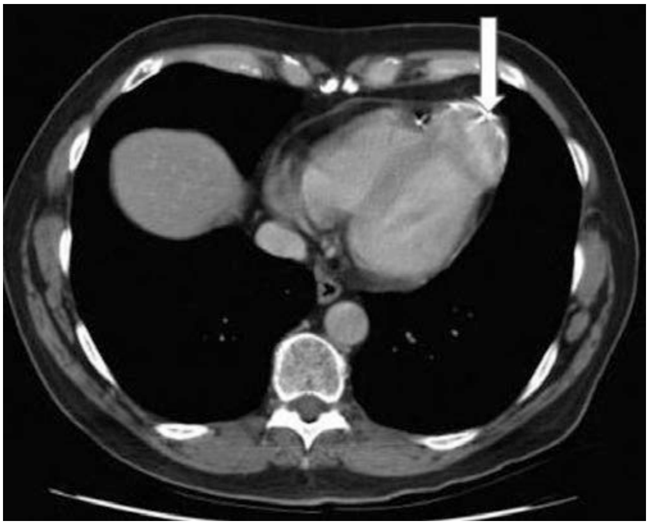

Fig. 26.5 Contrast-enhanced CT image demonstrating apical aneurysm with calcification (white arrow)

(Fig. 26.5). To differentiate a true aneurysm from a pseudoaneurysm with CT requires identifying the small ostium that connects the aneurysm with the left ventricular cavity. False aneurysms are usually substantially larger than true aneurysms; they frequently arise from the posterior or inferior wall of the left ventricle.

False-positive and false-negative findings are infrequent in cases of ventricular aneurysm.

Magnetic Resonance Imaging

MRI is a reliable, noninvasive modality for identifying left ventricular aneurysms and for assessing resectability. As with CT, dark-blood imaging may be employed to define the anatomy. Dynamic bright-blood imaging helps in defining blood pool motion; it is particularly useful in delineating the bulging of the aneurysm [25] (Fig. 26.6).

MRI scar mapping with delayed enhancement shows the location and transmural extent of scar tissue. Collagen retains the intravenously administered gadolinium-based contrast agent. MRI strain mapping may be used to distinguish those units of myocardium in which contractile function is retained from those units in which tethering occurs. MRI stripe tagging may depict pericardial adhesions.

MRI T2$*$ imaging helps in identifying thrombus; specific contrast agents may be used to define thrombi precisely. MRI may be performed to measure the model-independent ejection fraction and to estimate the degree of improvement after aneurysmectomy. MRI is the best modality for visualizing the pericardium [26, 27].

The degree of confidence in MRI is high, but the rates of false-positive and false-negative findings are high as well.

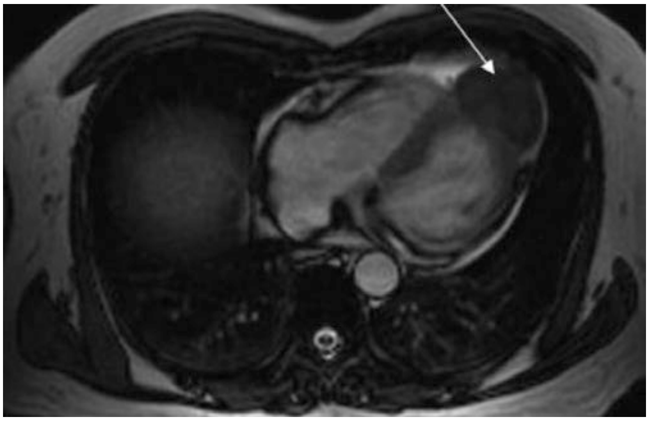

Fig. 26.6 MRI scan showing true aneurysm of the left ventricle with thrombus (white arrow)

Management

Pseudoaneurysm

Surgery

Once the diagnosis of pseudoaneurysm is established, surgical correction is usually mandatory. Surgery is urgently recommended when a pseudoaneurysm is discovered within the first 2–3 months after myocardial infarction because the onset of rupture is unpredictable [28]. However, when the diagnosis is made years after myocardial infarction or surgery, the urgency and even the need for operation is determined by symptoms rather than by risk of rupture. If there is preoperative hemodynamic instability, intra-aortic balloon pump should be inserted as early as possible to achieve hemodynamic stability. The size and location of the pseudoaneurysm determine the surgery. Median sternotomy with cardiopulmonary bypass assistance is the preferred approach. If there is a small chronic neck, direct neck ligation can performed. In patients with a defect located close to the basal part of the left ventricle, the ventricular defect is closed with a patch of Gore-Tex or Dacron to avoid potential distortion of the valvular structures or excessive traction on the edges of the defect. In case of post-infarction rupture, concomitant coronary artery bypass grafting is generally performed, in the presence of significant coronary artery disease, to improve the curative effect, reduce recurrence, and patch tear at the same time [28].

Transcatheter Device Closure

Although the conventional treatment is surgical intervention, transcatheter device closure, first described in 2004, is emerging as a new alternative for high-risk surgical candidates [29, 30]. Currently, the experience is still limited to a few reports. As there is little guidance in the literature, device selection needs to be individualized depending on the location and size of the pseudoaneurysm, and adjacent structures.

Several individual case reports have described the successful use of septal occluders, ventricular septal defect occluders, and coils. The margins may be necrotic and friable and give way during device placement or subsequently. To reduce device instability and the associated risk of device dislodgement, oversize ratios of 1.2–2.0 have been reported for the Amplatzer septal occluder in previous studies [30].

True Aneurysm

Surgical Indications

The presence of left ventricular aneurysm alone is not a surgical indication. Surgery is indicated when concomitant, persistent angina, refractory heart failure, thromboembolism, or life-threatening tachyarrhythmias occur [31]. Myocardial revascularization is typically performed at the time of aneurysmectomy.

Surgical Techniques

The first successful surgical treatment of a left ventricular aneurysm, by Wieting in 1912, involved the ligation of a congenital form of left ventricular aneurysm [32]. In 1944, Beck described using the fascia lata to reinforce the aneurysm [33]. The first angiographic description of left ventricular aneurysm was published in 1951 [34]. In 1955, Likoff and Bailey [35] successfully resected a left ventricular aneurysm via thoracotomy, using a tangential clamp without cardiopulmonary bypass. Over the past six decades a variety of techniques have been reported in literature for the surgical management of left ventricular aneurysms.

Plication

External plication without opening the aneurysm is a relatively simple technique that is currently reserved primarily for patients who have aneurysms of smaller dimensions that do not contain thrombi and for those who do not have severe left ventricular dysfunction or high end-diastolic pressure. The repair involves a double-layered suture from one side of the aneurysm to the other; a strip of Teflon is used on both sides and is oriented to reconstruct a normal ventricular shape. Usually, the area of repair does not include the entirety of the aneurysmal tissue [36].

Cooley Technique

Contemporary treatment of left ventricular aneurysms began in 1958, when Cooley and associates [37] performed a "linear" or "sandwich" repair of a larger aneurysm using cardiopulmonary bypass. For the next 30 years, the technique changed very little from the one Cooley described. Specifically, after longitudinal incision of the aneurysm and removal of any thrombi, the wall of the aneurysm was resected (usually parallel to the LAD or posterior descending artery, depending on aneurysm location) [37] (Fig. 26.7). A border area <2 cm from the scar tissue was left to enable the reconstruction of normal left ventricular

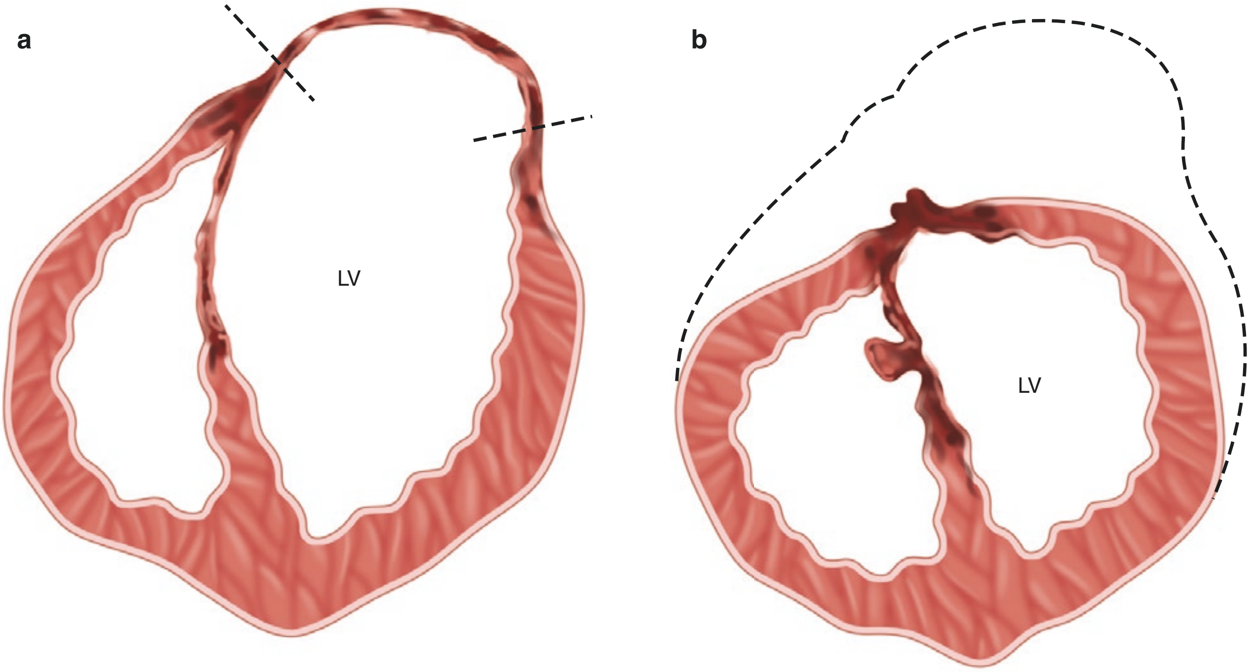

Fig. 26.7 Cooley technique ("linear" or "sandwich" repair). (**a**) Aneurysmal left ventricular (LV) cavity. (**b**) LV cavity after linear repair. The lateral and medial (septal) walls are sutured together at a point where they normally would be separated by several centimetres, resulting in non-anatomic geometry

geometry. Particular attention was paid not to resect too much of the aneurysmal wall, to avoid excessively reducing the size of the ventricular cavity. The resected area was closed vertically on either side, between two external strips of Teflon or pericardium: first, with a two-layer horizontal mattress suture, and then with a two-layer vertical running suture. A disadvantage of linear repair was that the lateral and medial (septal) left ventricular walls were sutured together, eliminating the natural separation of a few centimeters and leaving an area of akinetic myocardium that contributed to continued left ventricular dysfunction. The technique also failed to exclude an area of the involved septum [36].

Stoney Technique

Stoney and colleagues [38] showed that patients whose aneurysms were resected with the Cooley technique had incomplete reduction of the aneurysm, leaving an area of akinetic myocardium at the level of the interventricular septum, resulting in functional and volumetric impairment of the left ventricle. Therefore, Stoney introduced a new correction technique that involved the advancement and connection of the lateral myocardial wall with the border area between the viable tissue and the necrotic scar of the interventricular septum, but it omitted the revascularization of the affected area [38]. This technique also excluded the possibility of left anterior descending (LAD) artery revascularization because of its inclusion in the repair.

Jatene Technique

The Jatene technique involves opening the aneurysm, inspecting the internal cavity, and placing one or two purse-string sutures, mounted on pledgets, around the proximal portion of the aneurysm's ventricular septal aspect so that the size of the orifice can be reduced to that of the closure area. Septal plication is also performed to avoid septal dysfunction, and a ventricular Dacron patch is then stitched in the ventriculotomy orifice to stabilize the septum and restore the normal conical shape of the septum where it joins the ventricular wall. In this manner, the septum remains part of the left ventricular wall [39].

Dor Technique

After opening the aneurysm, the surgeon determines the extent of the endocardial scar and identifies the junction between the scar and the viable myocardium around the entire circumference of the aneurysm. The Dor technique—endoventricular circular patch plasty—involves placing a continuous 2–0 suture at this junction, deeply enough in the endocardium to prevent tears when the suture is tightened. The degree of suture tension determines the extent of the remaining opening in the ventricle and the size of the endocardial patch to be used. The patch is generally 2–3 cm in diameter and can be made of Dacron or pericardium. After the patch has been sutured inside the left ventricular cavity to close the endocardial opening, surgical adhesive glue is applied to reinforce the suture line (Fig. 26.8).

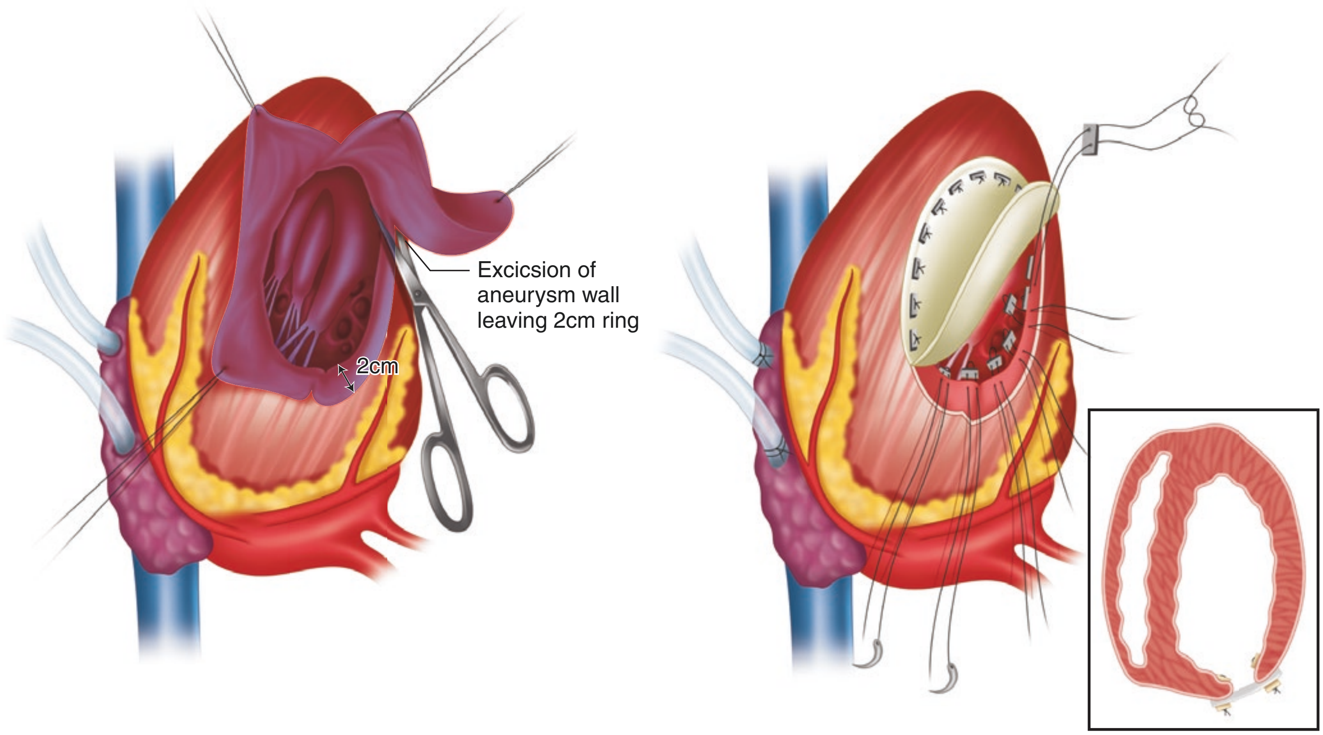

Fig. 26.8 Endoventricular circular patch plasty (Dor technique)

The Dor technique has four advantages. First, it enables the akinetic segment of the interventricular septum to be excluded. Second, it produces a more physiologic geometric cavity. Third, it preserves the LAD for possible grafting. Fourth, it eliminates the need for external prosthetic materials, which can cause persistent pericardial adhesions [40]. The exclusion of the ischemic interventricular septum and the reduction of ventricular volume enable a realignment of the myofiber cells of the remaining adjacent and viable remote myocardium [41].

The Dor technique differs from the Jatene technique in that the aneurysmal portion of the distal septum is excluded by placing an endocardial patch at the junction of the septal endocardial scar tissue and the normal septal endocardium [42]. The two techniques also differ in the positioning of the purse-string sutures relative to the septum. In the Jatene technique, the purse-string sutures are placed more proximally on the free wall of the LV and the septum, whereas in the Dor technique, they are placed a little more distally over the ventricular free wall and on the septum. Both use patches during final closure. Thus, the Jatene technique leaves the apical position of the ventricular cavity unchanged when compared to the septal position, whereas the Dor technique moves the apex of the ventricular cavity to a more lateral position in relation to the septum [42].

McCarthy Technique

In 1997, McCarthy and colleagues [43, 44] described an endoventricular circular plasty technique that eliminated the patch. The McCarthy technique involves opening the left ventricular apex at least 1.5–2 cm from the LAD. Visual inspection and palpation then enable identification of the border between the scar tissue and the contractile myocardium. This border is most easily recognized when the inspection is performed on a beating heart. If the surgeon determines that endoventricular circular plasty can be done without aortic clamping, myocardial ischemia can be avoided.

A 2-0 polypropylene, purse-string suture is first placed around the entire base of the aneurysm, deep into the scarred tissue, in order to apply considerable tension to the scar area. The suture is then tied from the inside on a Teflon pledget in an attempt to restore the geometry of the ventricular cavity. The degree of tension with which the suture is tightened determines the size of the remaining opening of the ventricle. If the opening is wider than 3 cm, a second purse-string suture is placed 4 mm distal to (above) the first one. When the ventricular opening remains greater than 3 cm, a patch is required, and closure is achieved with the Dor technique. Otherwise, the ventricular free wall is successively approximated, and two strips of Teflon are secured on either side of the opening with interrupted mattress sutures. Finally, the closure is reinforced with 3-0 polypropylene continuous suture [43, 44]. This procedure completely excludes the ischemic area and surrounds the left ventricular chamber with viable left ventricular muscle, except for a rim of scar at the repair site. Potential improvements to the technique include a less invasive ventricular remodeling technique that does not necessitate opening the left ventricle or using cardiopulmonary bypass. In the future, a thoracoscopic approach might be adopted [13].

Outcomes

Outcomes of the surgical techniques have been reported in the literature; however, they are difficult to interpret because of variations in the patient populations undergoing the procedures and the evolution of surgical techniques [45]. Many of the existing studies are single-centre, retrospective, or nonrandomized, and many are either uncontrolled or use historical controls. Only a few randomized, controlled studies have been performed, and some of these have had enrolment problems or issues with inclusion criteria [13]. The in-hospital mortality rates for patients undergoing these procedures range from 2% to 19%, with a mean of approximately 10% [46]. Risk factors for early death include severe left ventricular failure, myocardial infarction, and intractable arrhythmias. Risk factors for late death include incomplete revascularization and reduced systolic function of the basal segments of the left ventricle and the interventricular septum. After 5 years, the survival rate is approximately 69% for patients undergoing aneurysmectomy and either revascularization or mitral valve replacement, compared with 57% for those undergoing aneurysmectomy alone [46].

Conclusion

Contained rupture of the left ventricle by the adhering pericardium creates a pseudoaneurysm. This condition warrants emergency surgery. On the other hand, true left ventricular aneurysm is the discrete thinning of the ventricular wall (<5 mm) with akinetic or dyskinetic wall motion causing an out-pouching of the ventricle. Given the propensity for pseudoaneurysms to rupture leading to cardiac tamponade, shock, and death, compared with a more benign natural history for true aneurysms, accurate diagnosis of these conditions is important. Surgical treatment of true aneurysms is indicated in established cases of congestive heart failure, angina pectoris, malignant ventricular arrhythmia, or recurrent embolization from the left ventricle. The goal of surgical intervention is to correct the size and geometry of the left ventricle, reduce wall tension and paradoxical movement, and improve systolic function. Surgical techniques for repair of left ventricular aneurysm have evolved over the last six decades with endoventricular circular patch plasty as the preferred option.

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Coronary Endarterectomy

27

Nikolaos A. Papakonstantinou

High Yield Facts

- Coronary endarterectomy, firstly described by Bailey et al in 1957, is not an alternative but an adjunct to coronary artery bypass grafting.
- Coronary endarterectomy is the removal of the coronary atherosclerotic core through an arteriotomy either by traction (closed technique) or under direct vision (open technique) to achieve complete myocardial revascularization.
- Due to coronary endothelium removal, a coagulation cascade is triggered, so thromboprophylaxis by a single or double antiplatelet regimen with or without anticoagulation treatment is required.
- Despite its promising potential for complete revascularization in diffuse coronary artery disease, its safety and effectiveness are still doubted due to increased mortality and perioperative myocardial infarction rates.
- More comorbidities and risk factors in coronary endarterectomy candidates are more likely to be the reason for worse outcomes being reported rather than the endarterectomy itself.
- Diffuse coronary artery disease affecting side branches, severe calcification and in stent restenosis following full-metal jacket procedures are its indications.
- Coronary luminal diameters below 1 mm, multiple sites of obstruction and pinching of side branches and diffuse coronary thread-like appearance can be the angiographic indications.
- Coronary endarterectomy can be safely performed either on-pump or off-pump.
- Multi-vessel coronary endarterectomy significantly worsens patients’ prognosis.
- Coronary endarterectomy should only be performed by highly experienced surgeons in a highly selected group of patients, when there is no other choice for achieving complete revascularization, as it is a technically demanding procedure.

Introduction

Coronary artery bypass grafting (CABG) is the standard of care in complex coronary artery disease (CAD). However, in the current era, percutaneous coronary intervention (PCI) is the first line treatment in patients with focal or localized CAD [1–3]. As a result, patients referred for surgical revascularization are not only older with more comorbidities but are also more likely to suffer from diffuse CAD [4–6]. Irrespective of these concerns, complete myocardial revascularization, including the left anterior descending artery (LAD), is the ultimate goal to achieve the best possible postoperative and long-term outcomes [1, 7] Standard CABG may fail in terms of complete revascularization in up to 25% of patients with diffuse CAD, who are thus considered inoperable [8]. Therefore, reassessment of a 60-year old surgical technique introduced by Bailey et al [9], coronary endarterectomy (CE), may expand surgical possibilities by removing the coronary atherosclerotic core through an arteriotomy [10, 11].

In its initial stages the accompanying morbidity and mortality discouraged its wide application despite its success in angina relief [9]. Particularly, LAD endarterectomy was considered technically difficult [12–14] with high operative mortality and perioperative myocardial infarction (MI) rates reported [15–18]. Hence, CE was reserved for those patients with diffuse CAD [19]. However, this old surgical technique has been revived recently with a lot of published data showing favorable long-term outcomes [19–26]. CE can be safely performed either during on-pump [20, 27] or off-pump CABG [28, 29].

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History

The history of CE (Fig. 27.1) dates back to1956 when Charles Bailey introduced it. He successfully performed the procedure on two patients at Hahnemann Hospital in Philadelphia, USA [9]. This fact renders CE one of the first surgical procedures for the treatment of severe atherosclerosis and myocardial ischemia [9, 30]. CE is even older than CABG itself, which was not developed until the 1960s. It was initially a lone procedure using a distal, blind, retrograde technique without heart-lung bypass [9, 31]. Antegrade endarterectomy under direct vision was firstly performed 2 years later, in 1958, by Longmire and colleagues [11]. The first case series of patients with CEs was published in 1970s, when Cheanvechai et al [14] presented the midterm results of 315 patients who underwent CE adjunct to CABG using saphenous vein grafts (SVGs) in 1975. They reported 1.27% in-hospital mortality rate, 4.8% perioperative MI rate and 76.3% patency rate at 13.1 months. Angina relief was noticed after CE and despite its initial failure to get established in clinical practice [18] due to its accompanying high perioperative MI [15] and postoperative morbidity and mortality rates [15, 32], it has been revived primarily due to the increasingly complex CAD cases in the current era. Nowadays, CE is an adjunct to on-pump or off-pump CABG with comparable results between these two procedures [33]. Although right coronary artery (RCA) was initially preferred due to less catastrophic thrombotic complications [31, 32], LAD is currently the target coronary vessel of choice for endarterectomy. In our era, CE is a valuable surgical strategy to achieve complete revascularization when diffuse CAD is present [33].

Techniques

Two different CE approaches are described: a closed one (traction technique) and an open one (direct vision technique) [1, 34]. However, the best approach remains debatable [19]. The arteriotomy on the coronary vessel is the common step irrespective of the procedure selected [15]. In the closed technique, a smaller arteriotomy is required through which the atherosclerotic core is removed by applying gentle steady traction proximally and distally [3, 36]. The ischemic as well as the whole procedure time can be shortened if two concurrent limited arteriotomies are used for coronary endarterectomy [37]. Although the closed technique is faster and the anastomosis of the graft is easier [9, 30, 38], insufficient endarterectomy is more likely to happen [1, 34]. The subsequent snowplow effect—occlusion of the distal LAD and its side branches—may occur [39]. Despite gentle traction applied on the proximal part of the atheromatous core in LAD, an intimal flap may be formed due to tearing off of its diagonal branches and septal perforators. Similarly, occlusion of the lumen may occur distally due to a thrombus or dissection [3, 37, 40].

On the other hand, in terms of open endarterectomy, the whole procedure is performed under direct vision. Atheromatous plaques are completely removed from both the main vessel and the side branches [41, 42]. As a result, open CE is preferred in case of incomplete removal of the atherosclerotic core via the closed approach [43] as well as previously inserted stents which firmly cling to the intima [44–46]. A longitudinal arteriotomy on the coronary vessel beyond the limits of the atheromatous plaque is performed

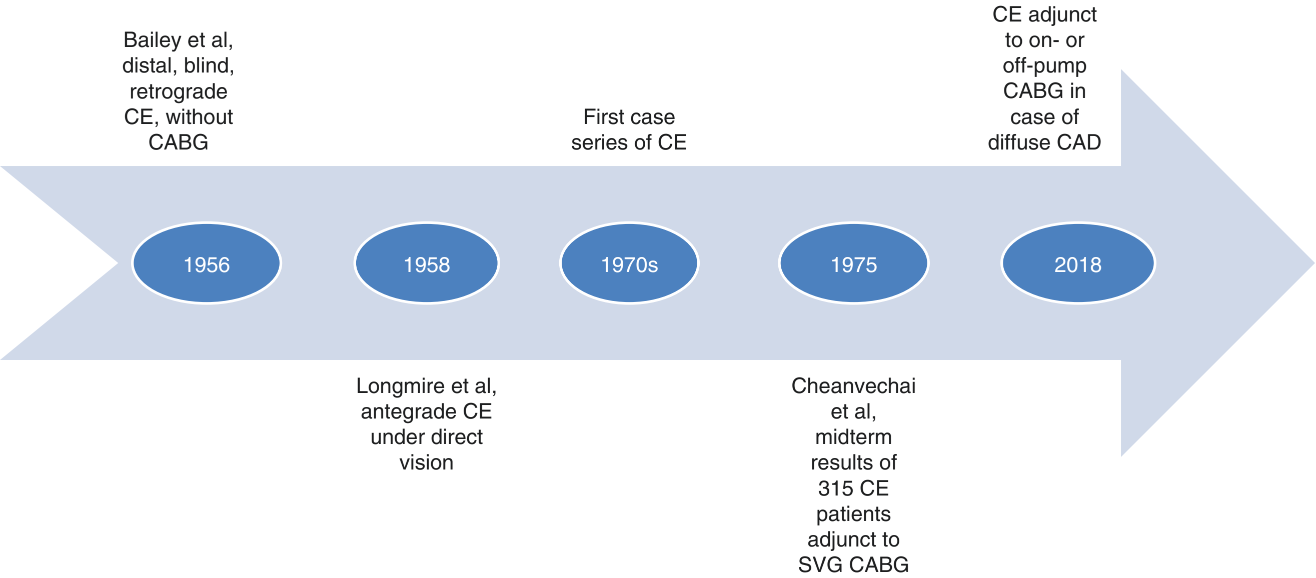
Bailey et al, distal, blind, retrograde CE, without CABG
First case series of CE
CE adjunct to on- or off-pump CABG in case of diffuse CAD
1956
1958
1970s
1975
2018
Longmire et al, antegrade CE under direct vision
Cheanvechai et al, midterm results of 315 CE patients adjunct to SVG CABG

Fig. 27.1 History of coronary endarterectomy. (*CABG* coronary artery bypass grafting, *CAD* coronary artery disease, *CE* coronary endarterectomy, *SVG* saphenous vein graft)

and the atherosclerotic plaque is removed [35]. Both the internal thoracic artery (ITA) and the SVG can be then utilized as an on-lay patch anastomosis to the LAD [36, 47]. A longitudinal saphenous vein patch covering the arteriotomy and a subsequent anastomosis of the left ITA on the aforementioned patch is an alternative approach [8]. Complete removal of the atherosclerotic plaque is achieved under direct vision while distal flow is secured in case of a dissection of the intima of the distal LAD [3]. Although more time is needed [3, 7, 19] and higher bleeding risk exists [48] intimal flap formation is prevented avoiding residual obstruction [1, 7, 19, 36] as well as distal myocardial ischemia [1]. According to Nishi et al [47], the open approach is superior to the closed one. Although the perioperative MI and 30-day mortality rates were similar between the two groups, patients subjected to open endarterectomy had a 5-year survival rate of 90.7%, compared with the 74% for the closed technique group. Morbidity rates were also superior in the open CE group in comparison with the closed one [47]. Finally, angiographic patency rate (78 patients at 21 ± 16 months) was superior in the open approach group (89.1% vs 81.0%) [47]. Therefore, although time consuming, open CE is the most advantageous endarterectomy approach [1].

Indications

Although its effectiveness is in doubt, [24, 26, 47, 49–51] patients having diffuse CAD and severe calcification of coronary arteries may benefit from CE [19] as neither PCI nor conventional CABG can achieve complete revascularization of the myocardium supplied by the affected side branches (diagonal and septal branches) [1, 34]. As a result, residual angina is possible [1, 3]. Additionally, conventional CABG in case of soft atherosclerotic plaques may result in embolization due to plaque rupture, whereas, in the presence of both soft atherosclerotic plaques as well as intense calcification, CE enables construction of a satisfying anastomosis [3]. Therefore, diffuse CAD affecting side branches with no option for conventional distal grafting and severe calcification of the LAD preventing construction of a simple anastomosis of the left ITA graft to the LAD are the main indications for CE [1, 3, 8, 10, 43, 52]. (Table 27.1). Moreover, in the current PCI era, delivery of multiple overlapping stents (full-metal jacket) to treat diffuse CAD is possible [53]. However, in-stent restenosis after full-metal jacket PCI is a real challenge [34]. Conventional CABG cannot achieve complete revascularization in case of these “stent-loaded” patients [44, 54]. Therefore, CE indications can be expanded to include patients with in-stent restenosis following full-metal jacket procedures [35, 45] (Table 27.1). En bloc long-segment stent removal by CE and subsequent surgical revascularization can be performed [55]. Coronary luminal diameters below 1 mm [3], multiple sites of obstruction and pinching of side branches and diffuse coronary thread-like appearance can be angiographic indications for endarterectomy [37] (Table 27.1). However, there is a lack of guidelines concerning CE indications [35]. The final decision for endarterectomy is made intraoperatively when the aforementioned findings are noted [3, 19, 36, 37].

Table 27.1 Coronary endarterectomy indications

Clinical	Angiographic
Diffuse coronary artery disease affecting coronary side branches	Coronary luminal diameters below 1 mm
Severe calcification of coronary arteries	Multiple sites of coronary obstruction
In-stent restenosis after full-metal jacket percutaneous coronary intervention (multiple overlapping stents)	Multiple pinching of coronary side branches
	Diffuse coronary thread-like appearance

Anticoagulation Protocol

Coronary endothelium is removed during CE. As a result, the subendothelial material is exposed to blood flow thus inducing coagulation cascade activation [3, 8, 56]. Therefore, thromboprophylaxis is a sine qua non in the medical management of CE patients. Although no guidelines exist on anticoagulation or antiplatelet management in patients subjected to CE [57, 58], there is a general consensus that a single or double antiplatelet regimen with or without anticoagulation treatment is required [7]. Various regimens have been recommended. Aspirin alone protocol lags behind due to disturbed endothelial integrity in case of CE thus failing to achieve long-term graft patency [20]. Either heparin infusion followed by warfarin for 3 months aiming at an international normalized ratio (INR) between 2.0 and 2.5 or double antiplatelet therapy (DAPT) immediately after the operation are reasonable [35] (Fig. 27.2). It is expected that complete neoendothelialization of endarterectomized vessels will occur within 3 months postoperatively [59]. Moreover, bleeding, tissue necrosis and hypersensitivity reactions are potential side effects of warfarin regimens [59]. Therefore, concurrent use of heparin, warfarin and aspirin is a recommended, complete anticoagulation protocol for endarterectomized patients. Heparin is withheld when an INR between 2 and 3 is achieved. Subsequently, discontinuation of warfarin 3 months postoperatively with permanent aspirin alone intake is recommended [3, 8, 19, 47, 59].

Replacing warfarin with clopidogrel is also reasonable after CE [36]. Clopidogrel is withheld 12 months postoperatively [60]. No need for INR control once weekly is the basic advantage of the latter regimen [59]. Even more aggressively, there are investigators favoring a triple anticoagulation therapy

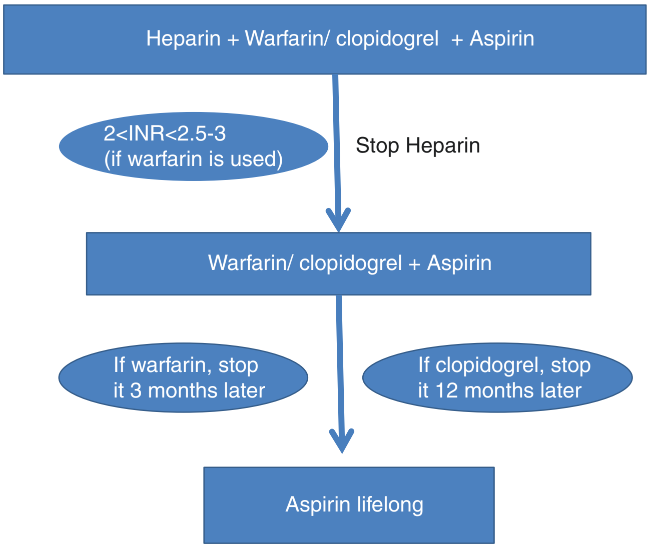

Fig. 27.2 Recommended anticoagulation protocol

(aspirin, clopidogrel, and warfarin). Warfarin and clopidogrel are discontinued 3 months and 1 year postoperatively respectively, and aspirin is continued lifelong [4, 34]. However, it is doubted if single versus double antiplatelet protocols can promote any difference in the early and late outcomes [61].

Safety of Coronary Endarterectomy

Incomplete revascularization after CABG due to diffuse CAD results in high operative and late mortality rates. Perioperative and late myocardial infarction rates, as well as reoperation rates are also increased. The catastrophic impact of incomplete revascularization gets even worse when the LAD is incompletely revascularized [24]. Consequently, patients with diffuse CAD should not be deprived of the possibility for complete revascularization via coronary endarterectomy [37, 62, 63]. Although, CE technique is more than half a century old [9], its safety and effectiveness are still doubted [15, 24, 26, 47, 49–51, 64, 65]. Despite its promising potential for complete revascularization in diffuse CAD, increased perioperative morbidity and mortality rates, as well as decreased long-term survival, particularly when the LAD is involved, are noted by some investigators as the major drawbacks [15, 64, 65]. Endothelium destruction subsequent to CE may trigger thrombogenesis or embolization of atheromatous debris may occur, leading to a deleterious postoperative MI [33]. As a result, no clinical recommendation of CE is included in the 2011 ACC/AHA Guideline for Coronary Artery Bypass Graft Surgery and 2014 ESC/EACTS Guidelines on myocardial revascularization [66, 67]. Thus, CE is only performed in highly selected patients when there is no other choice in some centres, whereas it is not at all performed in others [24].

Overall, mortality rates after CE are remarkably high compared to those after conventional CABG in international literature [12, 15, 20–23, 38, 49, 50, 52, 68–70]. The interpretation of the literature, however, is difficult because of great heterogeneity of the published studies.

Early studies (1975–1989) [10, 12, 14, 15, 18, 37, 64, 65, 71, 72] reporting outcomes of CE revealed in-hospital mortality up to 6.3% for single vessel CE or up to 10.4% for multi-vessel CE [65] (range 1.27–10.4%) [10, 12, 14, 15, 18, 37, 64, 65, 71, 72], perioperative MI up to 19% [71] (range 2.7–19%) [10, 12, 14, 15, 18, 37, 64, 65, 71, 72], re-occlusion rate up to 55% [64] and graft patency up to 85% at 60 months [10, 12, 14, 15, 18, 37, 64, 65, 71, 72]. Later studies (1990–2004) [8, 20, 21, 24, 26, 38, 41, 42, 50, 51, 68] showed better outcomes following CE. Operative mortality rates ranged from 1.2% to 6.5% [8, 51] whereas perioperative MI occurred in as low as 1.5% of patients according to Sommerhaug et al [41] and its occurrence did not exceed 8.1% according to other studies [8, 51]. Even better overall results have been published in recent studies after 2005 [2, 3, 6, 19, 22, 23, 29, 35, 47, 62, 63, 73–76]. Early mortality rates ranged from 1.4% to 6.3%, perioperative MI occurred in 1.5% to 6.4% of patients and graft patency rates were over 90% at about 2 years and over 56% at about 10 years. Interestingly, few studies showed a mortality rate over 3% in the last 5 years [25, 34, 36, 60, 75].

Soylu et al [76] and Wang et al [77, 78] conducted two meta-analyses comparing the short- and long-term outcomes of adjunctive CE to those of single CABG. The latter published a second meta-analysis comparing cardiovascular accidents between the two groups [69]. According to Soylu et al [76] comparing 7366 CABG along with CE cases to 47074 CABG only cases, concomitant CE significantly increased 30-day mortality, perioperative and postoperative MI when compared with CABG. Major postoperative adverse events including pulmonary complications, renal failure, ventricular arrhythmias, inotrope use and blood transfusion were also reported in the first group. In-hospital stay was also lengthened when compared with CABG only. Endarterectomized vessels also showed lower angiographic patency rates in the follow-up [76]. Similarly, Wang et al [77, 78] in their two meta-analyses (2712/17600 patients received CABG along with CE in their first study and 63730 patients in their second one) reported a correlation of the CABG along with CE group with worse outcomes with regard to cardiovascular accidents [78], as well as significantly higher 30-day postoperative all-cause mortality of the first group compared to CABG alone group. Thirty-day mortality outcomes were even worse in the subgroup of diffuse CAD of the LAD receiving CE [77]. Perioperative MI and 30-day postoperative complications were also significantly increased when CE was added to CABG. Interestingly, long-term survival was comparable [77].

The presence of more comorbidities and risk factors in CE candidates may account for higher mortality and morbidity for these patients rather than the endarterectomy itself [1, 3, 48]. According to Tiruvoipati et al [49], age, renal deficiency, diabetes mellitus, and decreased left ventricular function were independent risk factors for higher mortality rates after CE compared to conventional CABG rather than CE itself. Furthermore, perioperative MI, which is one of the most severe CE-related complications, is also increased [8, 12, 21, 22, 24, 38, 47, 50–52, 68, 70, 79, 80]. Improvement in surgical techniques has resulted in lower perioperative MI rates [48]. According to Shapira and colleagues [38], mortality and morbidity rates do not differ significantly between CE and conventional CABG and CE is not an independent predictor of perioperative MI. Finally, late graft patency rates after CE are rather satisfactory ranging from 40% to 81.5% [21, 26, 47, 50, 51]. Consequently, nowadays, CE is not an independent predictor of poor surgical outcomes [34].

Unresolved Issues

Single or Multi-vessel Coronary Endarterectomy

The more vessels are endarterectomized, the higher intra- and post-operative MI and mortality rates are reported [35, 65]. Single endarterectomy is associated with better results than multi-vessel endarterectomy [20, 33, 81]. RCA endarterectomy itself is related to excellent short-term clinical and angiographic results with no additional morbidity or mortality compared to non-endarterectomized RCA. However, according to Erdil et al [82], RCA endarterectomy as an adjunct to LAD or diagonal branch endarterectomy leads to increased early mortality. Single endarterectomy-associated early mortality rate was 3.3% against the 10.3% early mortality rate after double vessel endarterectomy according to Marzban et al [81]. Similarly, postoperative MI rates are also increased when a second coronary vessel is endarterectomized [81]. Single LAD CE is the preferred approach as LAD is very often visible along all its epicardial course, it can be easily and adequately stabilized, and less displacement of the heart is required resulting in minimum hemodynamic disturbance during off-pump CABG [36, 43].

Onlay-Patch Grafting Using the ITA

Whenever an extensive CE is required, either an on-lay patch using the ITA, or an SV patch and LITA grafting are the possible reconstruction approaches for adequate bypass grafting [7, 33]. Better patency rates, lower thrombogenicity and increased resistance to atherosclerosis are the advantages of the ITA on-lay patch [35]. Myers and colleagues [83] reported no significant impact on long-term survival after extensive CE of the LAD, irrespective of the choice of reconstruction method. On the contrary, ITA use was superior to SV use in terms of operative mortality, perioperative MI and long-term mortality according to Beretta and colleagues [42]. The superiority of the use of ITA was also obvious with regard to patency rate, survival rate and relief of symptoms [42]. Reduced mortality and longer cardiac event-free rates after CE of the LAD were also reported by Christenson et al when ITA was used [69]. Similarly, Soylu et al noticed an association between ITA use and better 30-day mortality, compared to the SVG and two vessel CE. Moreover, ITA grafting along with open CE resulted in improved graft patency [84].

Off-Pump Coronary Artery Bypass Grafting and Coronary Endarterectomy

Better outcomes of off-pump CABG encouraged CE performance on beating hearts. Favorable results of concomitant off-pump CABG and CE are reported in recent studies [28, 29, 85]. Consequently, the presence of a CPB circuit is not a prerequisite for performing CE [29]. Comparable morbidity and mortality rates after CE were reported either on- or off-pump by Naseri and colleagues [27]. According to Qiu et al, early and midterm angiographic patency rates were similar regardless of whether the procedure was performed on- or off-pump. No significant difference was reported either in terms of early mortality and perioperative MI between the two groups as well [86]. Similarly, Takahashi et al [36] examining 12 patients submitted to concomitant off-pump CABG and CE, reported neither in-hospital death nor any major morbidity including perioperative and postoperative MI. According to Soylu et al [33] studying nine observational studies, there was no significant difference in the outcomes between patients who underwent on- or off-pump CABG. Similarly, there was no difference in postoperative MI rates between these two methods [33]. According to the meta-analysis by Wang et al· [77] including 63730 patients, comparable outcomes in terms of mortality rates were also reported after CE regardless of if it was performed off- or on-pump [77]. Although data, including two case series published by Fukui et al (12 patients) [45] and Nishigawa et al (11 patients) [87], is scarce, minimal complications and satisfying patency rates have also been achieved in full-metal jacket cases operated with off-pump CE [45, 87].

Alternative Procedures

Several alternative procedures instead of CE have been proposed. Percutaneous transluminal coronary rotational atherectomy (PTCRA) is one of them. It can be performed as a single procedure or along with balloon angioplasty (PTCA) [88].

Its effectiveness was proven by a Cochrane review article in 2003 [89] and its update in 2012 [90]. Wasiak et al [90] showed no additional benefit of PTCRA compared to PTCA among 3474 patients from 12 trials in terms of restenosis at 6 months and at 1 year and in terms of in-hospital major complications including MI, emergency cardiac surgery or death. The authors concluded that PTCRA may be useful in case of PTCA failure in patients who are not candidates for surgery [90]. Another alternative approach in diffuse CAD is excimer coronary laser atherectomy (ECLA) delivering ultraviolet B light pulses to the atheromatous plaque [91]. Promising results were reported by Fernandez et al in their 4-year retrospective analysis including 58 cases [92]. Nevertheless, there is a prerequisite for ECLA. The wire should be able to pass through the plaque thus excluding totally occluded vessels from this approach [91].

Conclusions

When complete revascularization is threatened due to diffuse calcifications or because of diffuse atheromatous plaques affecting the coronary side branches, CE constitutes a valuable surgical option. Acceptable mortality, morbidity, and angiographic patency rates are reported for CE, regardless of the coronary vessel endarterectomized and the choice of surgical technique, as well as whether or not CPB is used. However, multi-vessel CE significantly worsens patients' prognosis. As it is a technically demanding approach, it should only be performed by highly experienced surgeons. Moreover, CE should be offered to a highly selected group of patients to achieve complete revascularization. CE is not an alternative but an adjunct to CABG treatment. It should only be undertaken when the artery to be endarterectomized supplies blood to a coronary bed of at least moderate size, while open CE is the indicated surgical approach for dealing with full-metal jacket LAD.

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28

Transmyocardial Laser Revascularization

Justin G. Miller and Keith A. Horvath

High Yield Facts

- Transmyocardial laser revascularization (TMR) has emerged as a treatment modality for patients with refractory angina who have exhausted options for coronary artery bypass grafting and percutaneous coronary intervention.
- To date, there have been six prospective randomized controlled clinical trials published in peer-reviewed journals, in which over 1000 patients with refractory angina received either TMR (Ho:YAG or CO_2 laser) or medical management.
- TMR has been performed in over 100,000 patients worldwide.
- TMR can be performed through a thoracotomy incision without the need for cardiopulmonary bypass or anticoagulation.
- The likely mechanism is the stimulation angiogenesis as a result of the TMR channels.
- TMR patients are more likely to be free from angina symptoms (33% vs 11%, p = 0.02) compared with medical management patients at a mean of 5 years.
- Long-term survival for TMR patients is higher than medical management alone (65% vs 52%; p = 0.05) at a mean of 5 years.
- Patients who undergo TMR and coronary artery bypass grafting (CABG) have a reduced operative mortality rate (1.5% vs 7.6%, p = 0.02) and reduced postoperative inotropic support requirements (30% vs 55%, p = 0.001) versus CABG alone.
- Patients treated with TMR and CABG have an increased 30-day freedom from major adverse cardiac events (97% vs 91%, p = 0.04) and improved 1-year Kaplan-Meier survival (95% vs 89%, p = 0.05) versus CABG alone.

Introduction

Although the techniques of coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) have improved over time, there are an increasing number of patients with diffuse coronary artery disease (CAD) and refractory angina who have exhausted their options for revascularization [1–3]. Incomplete revascularization not only leads to hospitalizations for unstable angina but is also a strong predictor of morbidity and mortality [2, 4].

Novel therapeutic modalities are being used in these patients with the goal of treating symptoms from incomplete revascularization. Some of these treatments include transmyocardial laser revascularization (TMR), stem cell therapy, spinal cord stimulation, and external counterpulsation [3]. Of these TMR has been performed on over a 100,000 patients worldwide. TMR was approved by the US Food and Drug Administration in 1998 to treat moderate to severe angina resulting from CAD not amenable to medical therapy, PCI, or CABG. While TMR can be performed in conjunction with other procedures, such as CABG, sole TMR can be performed through a thoracotomy incision without the need for cardiopulmonary bypass or anticoagulation [5–14]. Additionally other methods for TMR have been investigated, such as percutaneous TMR [15–18].

Mechanism for Clinical Efficacy

Investigators have proposed multiple methods to create transmural channels in myocardium, such as ultrasound,

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cryoablation, radio frequency, heated needles, hollow and solid needles, and lasers, to allow direct perfusion of the myocardium via transmural channels in the ischemic myocardium [19–24]. The creation of transmural channels was based on the reptilian circulation, in which sinusoids allow blood from the ventricles to directly perfuse the myocardium as the coronary circulation is fairly rudimentary and only supplies a thin layer of the epicardium. Of the aforementioned methods, only laser TMR has demonstrated significant clinical results. However, there have been conflicting data regarding the long-term patency of the TMR channels. While some clinical trials and experimental work have demonstrated long-term patency [25–30], some autopsy series and laboratory data indicate that the channels do not remain patent [31–35]. Regardless, channel patency is likely not the principal mechanism of efficacy of TMR.

Proposed mechanisms include myocardial denervation and myocardial angiogenesis. Denervation may lead to anginal relief by damage to the sympathetic nerve fibers. However, there has been conflicting experimental evidence regarding denervation [36–40]. This has been noted in clinical trials, such as evidence of sympathetic denervation on positron emission tomography (PET) scanning of Holmium:yttrium aluminum garnet (Ho:YAG) TMR treated patients [41]. The most likely mechanism for the clinical efficacy of TMR is the stimulation of angiogenesis as a result of the TMR channels. This results in improvement of symptoms over time as well as concomitant improvement in perfusion and is demonstrated histologically [32, 34, 42–48] as well as biochemically by an upregulation of vascular endothelial growth factor messenger ribonucleic acid, expression of fibroblast growth factor 2, and matrix metalloproteinases following TMR [49–51]. Functional improvement has been demonstrated subjectively with quality of life assessments and objectively with dobutamine stress echocardiography, PET, and cardiac magnetic resonance imaging [52–55].

Devices

Numerous wavelengths of laser light have been used experimentally, such as xenon-chloride, Neodymium:YAG, Erbium:YAG, Thulium-Holmium-Chromium:YAG, carbon dioxide (CO_2), and Ho:YAG lasers [56–61]. However, only the Heart Laser CO_2 Transmyocardial Revascularization System (Novadaq Technologies Inc., BC, Canada) and the SolarGen TMR Ho:YAG Laser System (CardioGenesis Corporation, Foothill Ranch, CA, USA) are currently FDA-approved and being utilized for TMR. These two devices utilize different wavelengths and energy output as well as slightly different surgical techniques [11, 62].

The CO_2 laser energy is delivered via hollow tubes and is reflected by mirrors to reach the epicardial surface (Figs. 28.1 and 28.2). 1-mm channels are made with a 15–20 J pulse with pulse duration of 20–40 ms. The firing of the laser is synchronized to occur on the R-wave of the electrocardiogram cycle for maximal ventricular filling. Transesophageal echocardiography (TEE) can be used to confirm accurate transmural channel formation, as a result of vaporization of blood within the ventricle [60]. The Ho:YAG laser uses pulsed laser beam sequences of 1–2 J and achieves a 1-mm channel by manually advancing a fiber bundle through the myocardium while the laser fires at a rate of five pulses per second [56].

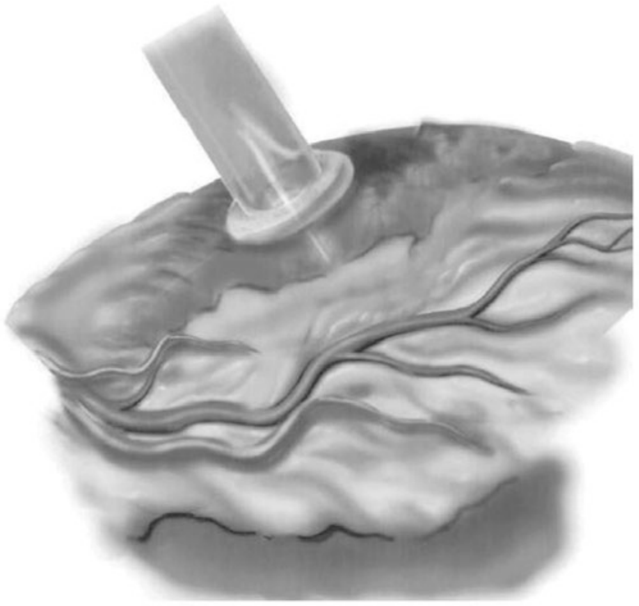

Fig. 28.1 The CO_2 laser energy is delivered via hollow tubes and is reflected by mirrors to reach the epicardial surface

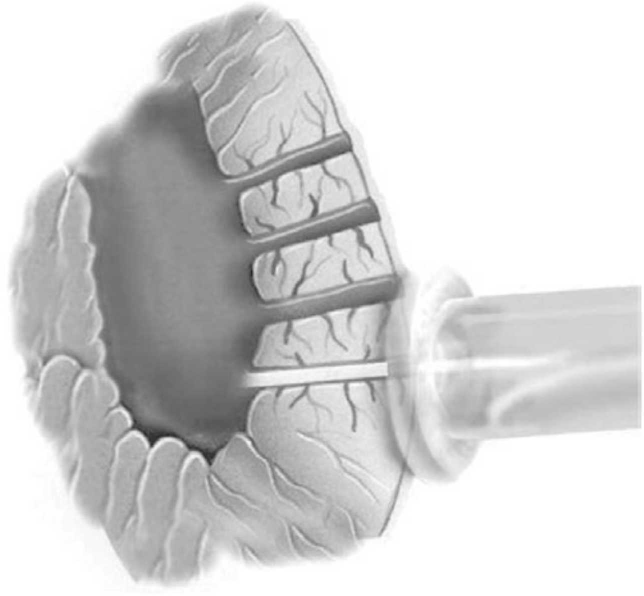

Fig. 28.2 Energy from the CO_2 laser creates a transmural channel in a single 20-J pulse

Operative Technique

A left anterior thoracotomy in the fifth intercostal space is the preferred incision site (Fig. 28.3), as the inferior and posterior lateral portions of the heart can be reached through this incision with a combination of manual traction, placement of packs behind the heart, and the use of a right-angled laser handpiece (Fig. 28.4). Channels are created starting near the base of the heart and then serially in a line approximately 1-cm apart toward the apex; starting inferiorly and working superiorly to the anterior surface of the heart. Some bleeding is encountered from the channels, therefore proceeding inferiorly to superiorly keeps the anterior area clear and expedites the procedure. The number of channels created depends on the size of the heart and on the size of the ischemic area. Myocardium that is thinned by scar, particularly when the scar is transmural, should be avoided as TMR will be of no benefit to these regions and bleeding from channels in these areas may be problematic. The thoracotomy is then closed after the placement of a chest tube and, in the majority of the cases; the patient is extubated in the operating room.

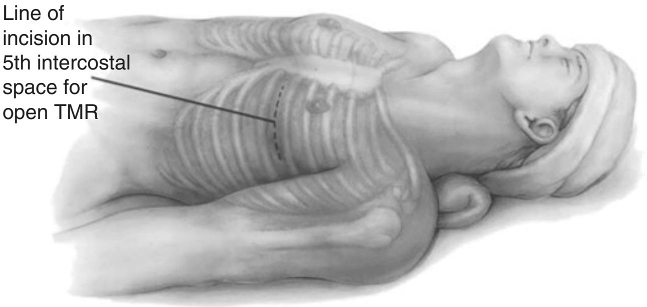

Fig. 28.3 Sole therapy transmyocardial laser revascularization performed as an open surgical procedure is typically done through a left anterolateral thoracotomy in the fifth intercostal space. Exposure of the heart through this incision can typically be achieved without division of the ribs or costal cartilages

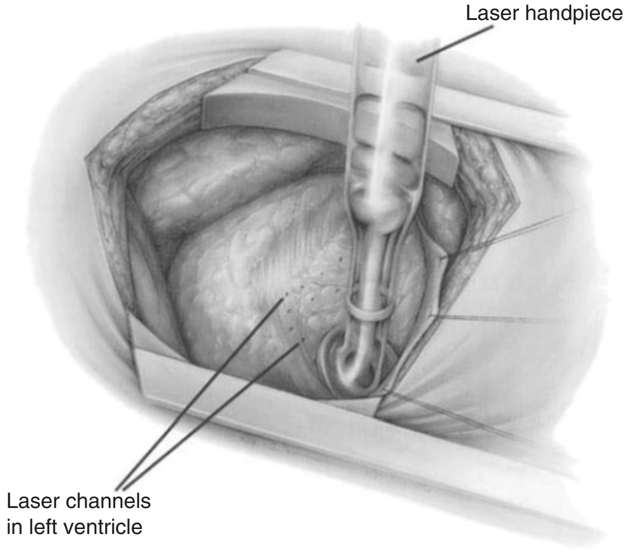

Fig. 28.4 Channels are created one per square centimeter, beginning inferiorly and moving superiorly to the anterior section of the heart. Total channel number depends on size and ischemic territory

Clinical Trials

TMR as Sole Therapy

Initial non-randomized trials demonstrated that sole therapy TMR could be performed safely on patients with CAD who previously had no other options because either their CAD was not amenable for revascularization or the patients were deemed high risk for revascularization [5–7]. The significant angina relief achieved in these patients led to prospective randomized controlled studies to further demonstrate the efficacy of TMR [8–13].

To date, there have been six prospective randomized controlled clinical trials published in peer-reviewed journals, in which over 1000 patients with refractory angina received either TMR (Ho:YAG or CO_2 laser) or medical management. Three studies utilized a Ho:YAG laser [8–10] and three implemented a CO_2 laser [11–13]. All of the patients had preoperative evidence of reversible ischemia based on myocardial perfusion scanning. There were no significant demographic differences between the TMR and the control groups for any of these trials. Most of the patients were Canadian Cardiovascular Society (CCS) Angina Class IV (61%) and the ejection fractions were mildly diminished at 48 ± 10%. Many of the patients had suffered at least one previous myocardial infarction and most had some prior revascularization. Two of the trials permitted a crossover from the medical management group to laser treatment. Criteria for crossover included the presence of unstable angina that necessitated intravenous anti-anginal therapy for which they were unable to wean over a period of at least 48 h. These crossover patients were less stable and significantly different than those who had been initially randomized to TMR or medical management alone [8, 11].

The endpoint for all six clinical trials was the change in angina symptoms. Validated standardized questionnaires such as the Seattle Angina Questionnaire, the Short Form Questionnaire 36, and the Duke Activity Status Index were also utilized to detect changes in symptoms and quality of life. Objective measurements consisted of repeated exercise tolerance testing as well as repeat myocardial perfusion scans. Patients were reassessed at 3, 6, and 12 months post-randomization.

Perioperative mortality rates ranged from 1–5%. One-year survival for TMR patients was 84–95% and for medical management patients were 79–96% [8–13]. Meta-analysis of

Table 28.1 One-year success rate for randomized trials of transmyocardial revascularization (TMR) versus medical management (MM)

Study	Laser	MM (%)	TMR (%)
Aaberge et al. [13]	CO_2	0	39
Schofield et al. [12]	CO_2	4	25
Burkhoff et al. [9]	Ho: YAG	11	61
Frazier et al. [11]	CO_2	13	72
Allen et al. [8]	Ho: YAG	32	76

Success rate = proportion of patients who experienced a decrease of two or more angina classes

the 1-year survival demonstrated no statistically significant difference between the patients treated with a laser to those that continued with their medical therapy [15]. Using a definition of success as a decrease of two or more angina classes, all of the studies demonstrated a significant success rate after TMR from 25–76% (Table 28.1) and a meta-analysis of this angina reduction yielded a summary odds ratio of 9.3 (95% CI: 4.6–18.5; $p < 0.000001$) [62]. Significantly fewer patients in the medical management group experienced symptomatic improvement and the success rate for these patients ranged from 0–32% [8–13].

Quality of life indices also demonstrated significant improvement for TMR treated patients over medical management in every study. Global assessment of myocardial function by ejection fraction using echocardiography or radionuclide multi-gated acquisition scans showed no significant change in the overall ejection fraction for any of the patients, regardless of group assignment or study. A meta-analysis of the 1-year hospitalization rate of patients in the laser treated group was statistically significantly less than for those treated medically. Medical management patients were admitted four times more frequently than TMR patients over the year of follow-up [15].

Exercise tolerance testing was also performed in three of the trials with an improvement demonstrated for TMR treated patients [9, 12, 13]. Two studies showed an average of 65–70 s improvement in the TMR group at 12 months compared to their baseline, while the medical management group had either an average of 5-s improvement or a 46-s decrease in exercise time over the same interval [12, 13].

Myocardial perfusion scans were obtained preoperatively to verify the extent and severity of reversible ischemia. Four of the trials included follow-up scans as part of their study [8, 9, 11, 12]. While the methodology differed, the results demonstrated an improvement in perfusion for CO_2 TMR treated patients. One CO_2 study demonstrated a significant decrease in the number of reversible defects for both the TMR and the medical management patients [12]. This improvement in the reversible defects in the TMR group was seen without a significant increase in infarcts at the end of the study. However, the number of fixed defects in the medical management group had nearly doubled over the same 12-month interval. Similarly, there was a 20% improvement in the perfusion of previously ischemic areas in the CO_2 TMR group of another trial and in that same trial, there was a 27% worsening of the perfusion of the ischemic areas in the medical management group at 12 months [11]. There was no difference in the number of fixed defects between the groups at 12 months, nor was there a significant change in the number of fixed defects for each patient compared with their baseline scans in that report. The remaining two Ho:YAG studies that obtained follow-up scans showed no significant difference between the TMR and the medical management groups at 12 months and no significant improvement in perfusion in the TMR treated patients over the same interval [8, 9].

Two reports of long-term follow-up demonstrated that angina symptoms were still significantly improved (24% vs 3%; $p = 0.001$) and unstable angina hospitalizations were significantly reduced ($p < 0.05$) at a mean follow-up of 43 months compared to medical management [63]. TMR patients continued to experience at least two-class angina improvement from baseline compared to medical management patients (88% vs 44%; $p < 0.001$). TMR patients compared to those medically managed were also more likely to be free from angina symptoms altogether (33% vs 11%; $p = 0.02$) at a mean of 5 years. In addition, long-term survival for TMR patients was reported as 65% vs 52% for medical management patients ($p = 0.05$) [64].

Follow-up of a series of nonrandomized patients who received TMR and survived long term also supported these findings. At a mean of 5 years and up to 7 years post-procedure, 81% of these patients improved to CCS Class II or better, 68% were found to have improved at least two angina classes from baseline, 17% were angina-free, and quality of life remained significantly improved [21].

TMR as an Adjunct to CABG

TMR has also been evaluated in conjunction with CABG in patients with CAD which would be incompletely revascularized by CABG alone. The safety and effectiveness of adjunctive TMR have been somewhat difficult to assess with the effect of CABG and the lack of randomized control arms in some studies [65–67].

Two prospective, randomized, multi-centered controlled trials have been performed using TMR and CABG. In these studies patients with one or more viable myocardial target areas served by coronary vessels that were not amenable to bypass grafting received CABG plus TMR or CABG alone. Baseline and operative characteristics were similar between groups, including the location and number of bypass grafts placed (3.1 ± 1.2 for CABG/TMR versus 3.4 ± 1.2 for CABG alone; p = 0.07). Patients were blinded to their treatment group through 1-year follow-up [11, 68].

Results demonstrate improved outcomes following TMR and CABG versus CABG alone in terms of a reduced operative mortality rate (1.5% vs 7.6%; p = 0.02), reduced postoperative inotropic support requirements (30% vs 55%; p = 0.001), increased 30-day freedom from major adverse cardiac events (97% vs 91%; p = 0.04), and improved 1-year Kaplan-Meier survival (95% vs 89%; p = 0.05). At a mean of 5 years, both groups experienced significant angina improvement from baseline, however, the TMR + CABG group had a higher mean of angina-free patients (78% vs 63%; p = 0.08), compared to CABG alone patients. Long-term survival was similar between randomized groups [68].

Percutaneous Myocardial Laser Revascularization

Several catheter based percutaneous trials have attempted to demonstrate a symptomatic improvement with the creation of 2–3 mm deep subendocardial divots achieved with a laser fiber fed via a peripheral artery into the left ventricle [16–18]. The only double-blinded randomized controlled trial for percutaneous myocardial laser revascularization (PMR) randomized 298 patients to low-dose laser channels, high-dose laser channels, or a sham procedure. At 6 months, there were no differences in the change in exercise duration between the three groups (high-dose laser [28.0 s, n = 98]; low-dose laser [33.2 s, n = 98]; sham [28.0 s, n = 100]; p = 0.94). Conversely, the morbidity and mortality of PMR are reportedly similar to that seen with TMR [16].

Conclusions

Cardiothoracic surgeons are increasingly presented with complex patients who have developed diffuse CAD and have exhausted nonsurgical options. Results replicated in multiple randomized, controlled trials augmented by recently available long-term results have validated the safety, effectiveness, and substantially improved health outcomes through the application of TMR for the treatment of selected patients with severe angina due to diffuse disease, when used alone and as adjunctive therapy to achieve a more complete revascularization. Based on an assessment of the cumulative results from these multiple randomized trials, as well as practice guidelines from the American College of Cardiology/American Heart Association and Society of Thoracic Surgeons, the weight of the evidence strongly favors the use of TMR in the treatment of stable, medically refractory, angina patients [8–15, 62, 69].

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29

Gene Therapy for Coronary Artery Disease

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Abbreviations

ASPIRE	A randomized, controlled, parallel group, multicenter phase 3 study to evaluate the efficacy and safety of Ad5FGF-4 using SPECT myocardIal peRfusion imaging in patients with stable angina pEctoris
AWARE	Angiogenesis in women with angina pectoris who are not candidates for revascularization
cTnT	Cardiac Troponin T
FGF	Fibroblast growth factor
GMT	Gata4, Mef2c and Tbx5 cardiac reprogramming factors
HGH	Hepatocyte growth factor (HGH)
HIF-α	Hypoxia-induced factor alpha
iCMs	Induced cardiomyocytes
iPSCs	Induced pluripotent stem cells
KAT301	Kuopio Angiogenesis Trial 301
miRNA	Micro RNA
shRNA	Short hairpin RNA
TGF-β	Transforming growth factor beta
VEGF	Vascular endothelial growth factor

High Yield Facts

- Many patients with end-stage coronary artery disease do not have revascularization options due to small vessel disease and are not candidates for transplantation or mechanical circulatory support.
- Advances in cellular biology have unlocked the key genetic drivers of myocardial cell fate, and these can be utilized to reverse adverse remodeling in the ischemic heart.
- Several vectors can allow entry of genetic material into cells, with modified viruses being the most commonly utilized.
- Multiple routes of administration are possible, but local administration appears to have key pharmacokinetic advantages over systemic or intracoronary routes.
- Local administration can be achieved by direct epicardial injection via thoracotomy or catheter-based endocardial injection.
- Vascular endothelial growth factor (VEGF) is the key driver of angiogenesis, and can increase vessel density in target tissues.
- Gata4, Mef2c, and Tbx5 (GMT) compose the classic cocktail of reprogramming factors to convert host cells into induced cardiomyocytes (iCMs).

Introduction

Congestive heart failure is the common end point for advanced coronary artery disease (CAD) and the leading cause of mortality from heart disease [1]. Current therapies for end-stage coronary artery disease in addition to medical therapies include coronary bypass surgery (CABG), percutaneous coronary intervention (PCI), heart transplant and/or implantation of mechanical circulatory support (MCS) devices. These interventions, especially transplant and MCS procedures, are associated with considerable morbidity, cost

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and/or availability limitations, and aggregate 5-year mortality rates of up to 50% [2–4]. Furthermore, many patients are not candidates for such therapies and may therefore benefit from alternative therapies.

Native recovery after acute myocardial infarction/acute coronary syndrome (ACS) may be characterized by endogeneous myocardial revascularization via the process of collateral vessel formation and "biologic bypass" of obstructing coronary lesions, and/or pathologic ventricular remodeling of infarcted myocardium. The latter is associated with proliferation of endogenous cardiac fibroblasts and formation of myocardial scar tissue at the expense of functional cardiomyocytes [5]. Unfortunately, despite some evidence of limited endogenous myocyte replication or regeneration from resident stem cells, native adult cardiac muscle does not effectively regenerate itself *de novo* after cardiomyocyte death. Typically then, both native recovery mechanisms are incomplete and only partially resolve an ischemic and depressed cardiac functional state.

Initial strategies to address these biologic deficiencies focused on administering exogenous genes or stem cells (e.g., embryonic stem cells, mesenchymal stem cells or skeletal myoblasts) to induce new blood vessel growth (angiogenesis) into areas of myocardial ischemia or into infarct zone to enhance cardiac perfusion and function, respectively [6]. Angiogenesis trials were however unfortunately met with significant disappointment after the failure of poorly designed studies to produce significant improvements in myocardial perfusion, and stem cell clinical trials have been largely disappointing likely due to inadequate implant phenotypes and/or poor implant survival and engraftment into the host myocardium [7–9].

Cardiac gene therapy is the process of delivering local or systemic growth factors, genes or small molecules to myocardium to alter gene expression for the purpose of cardiac regeneration. Genes may be delivered to the heart to induce angiogenesis, reduce pathologic fibrosis, induce replication of endogenous cardiomyocytes or expansion of existing cardiac progenitor cells, which may differentiate into various cardiac subtypes [10] (Table 29.1). In the classic paradigm, a viral delivery vehicle introduces a dosage of genetic material into the target tissue to induce transformation of cell phenotype and mechanical function of myocardial tissue. This therapeutic approach carries potential for interrupting, and possibly even reversing, the inexorable decline of severe coronary artery disease into congestive heart failure. Despite discouraging initial efforts, current applications of cardiac gene therapy are showing increasing promise.

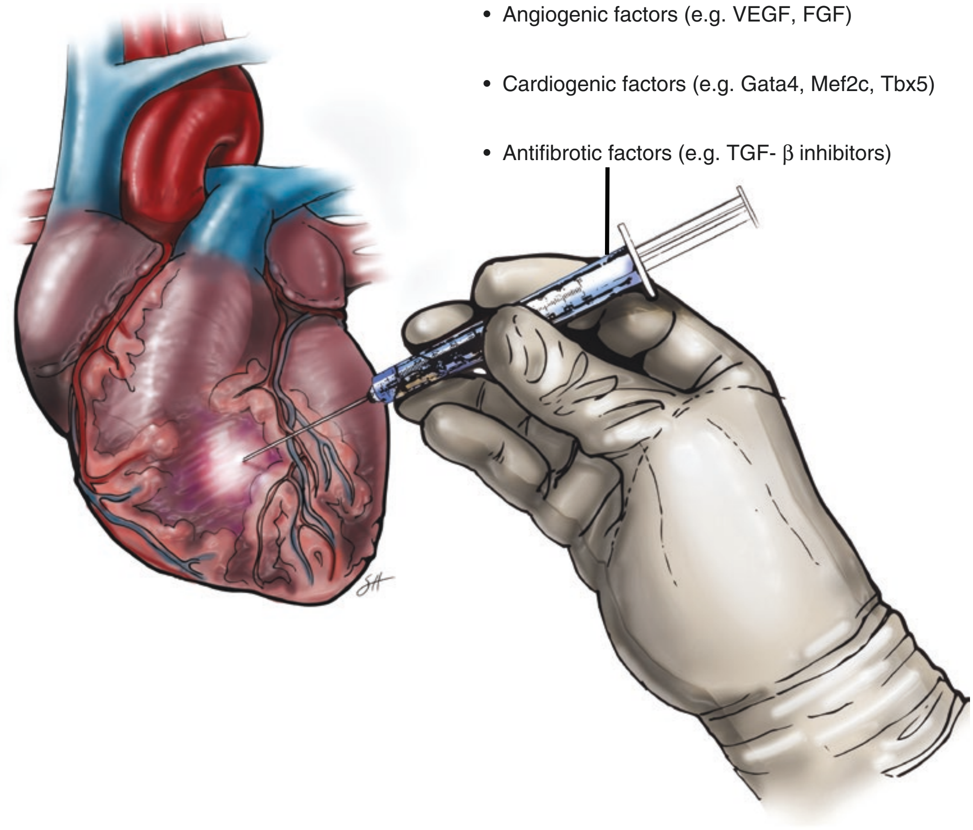
In particular, the recently introduced strategy of "cellular reprogramming" utilizes gene therapy to generate (induced) cardiomyocytes (iCMs) from endogenous scar fibroblasts [11, 12].

Clinical Gene Therapy—Past Lessons and Current Successes

The history of clinical gene therapy for cardiac regeneration parallels our increasing understanding of the molecular biology and, especially, the embryologic development of the heart, i.e. cardiogenesis. Initial attempts at cardiac regeneration using gene therapy were ushered in by Dr. Folkman's discovery in the 1970s that growth factors, now identified as vascular endothelial growth factor (VEGF), are associated with tumorigenesis and may potentially be useful in ischemic heart disease and ischemic limbs [13]. During a period of unrestrained enthusiasm for angiogenic gene therapy to regenerate myocardium, researchers performed hundreds of

Table 29.1 Gene therapy and stem cell applications for cardiac disease

Strategy	Description	Advantages	Disadvantages/Limitations
Revascularization (Angiogenic therapies)	Delivery of angiogenic factors (VEGF, FGF) for formation of new blood vessels in ischemic myocardium	Relatively efficient gene administration and effect	Limited data demonstrating efficacy
Stem cell implantation	Cardiomyocyte replacement using autologous or allogeneic stem cells	Avoids immunorejection (if autogenous cells)	Marginal improvement in ejection fraction (2–5% nominal increase) Low cell survival and implantation
Induced pluripotent (iPS) cell implantation	Cardiomyocyte replacement using patient-derived cells that have been reprogrammed into iPS cells	Potentially reduced immunorejection risk (if autogenous cells)	Risk of arrhythmia, teratoma Low cell survival and implantation
Cardiac progenitor cell implantation	Cardiomyocyte replacement using patient-derived cardiac stem cells	Avoids immunorejection (patient-derived cells that are re-implanted into the heart after treatment)	Similar to other cell implantation techniques
In situ direct cardiac reprogramming	Delivery of cardiogenic factors or genes to reprogram fibroblasts into cardiomyocytes	May abrogate exogenous stem cell administration disadvantages	Human cells resistant to reprogramming
Cardiomyocyte proliferation	Delivery of genes to induce replication of existing cardiomyocytes	May increase implant cell population	Very low efficiency



- Angiogenic factors (e.g. VEGF, FGF)
- Cardiogenic factors (e.g. Gata4, Mef2c, Tbx5)
- Antifibrotic factors (e.g. TGF- β inhibitors)

Fig. 29.1 Schematic of direct myocardial administration of gene vectors or other agents via epicardial (thoracoscopic or surgical) approach. *TGF-β* transforming growth factor beta, *VEGF* vascular endothelial growth factor, *FGF* fibroblast growth factor (Adapted from Patel VB, et al. [17])

clinical trials on over 2000 patients with overall mixed results [14, 15]. Retrospective analysis of these trials revealed critical inconsistencies in study design, controls and clinically relevant endpoints to measure outcomes, as well as a lack of pharmacokinetics data on the required "dose" of gene for efficacy and the best method of gene delivery [6, 14, 15]. Such shortcomings led to the generalized misconception that cardiac gene therapy was inefficacious, and ultimately set the field back. On the other hand, several new angiogenic gene therapy clinical trials are underway or are being contemplated that are designed to address past deficiencies in angiogenic clinical trial design.

The lessons learned from initial gene therapy trials have also informed the development of the novel gene therapy strategies of cardiac cellular reprogramming, which as opposed to exogenous stem cell delivery strategies offers the possibility of changing cardiac fibroblasts into induced cardiomyocytes in situ. In contrast to prior attempts, *in situ* cardiac cellular reprogramming has been developed on a robust platform with rigorous investigation of target genes (including specific combinations, stoichiometry), vectors (viral, micro RNA, and small molecules), and standardization of study design [5, 16–18]. Investigations have also expanded to include adjuvant therapies such as angiogenic factors, antifibrotic genes and downregulation of epigenetic barriers impeding reprogramming. Emerging evidence has indicated that these processes can work synergistically, and together may be capable of overcoming post-infarct cardiac remodeling leading to heart failure [5, 16–18] (Fig. 29.1).

Gene Delivery Vectors

Options for gene delivery in cardiac regeneration include the use of **plasmids**, integrative viruses (**Retrovirus**, **RV**, or **Lentivirus**, **LV**), non-integrative **adenovirus (AV)**, **adeno-associated virus (AAV)**, or **Sendai viruses (SV)**, **micro RNA** or **small molecules** [19–21] (Table 29.2). These agents may be delivered systemically or locally, most commonly through intramyocardial injection or intracoronary delivery.

Plasmids

Plasmids are circular DNA which can enter the nucleus for transcription by the host cell, and were implemented via intramyocardial injection in early angiogenesis trials utilizing VEGF for CAD [6]. A favorable safety profile was demonstrated, but results were largely equivocal given the poor efficiency of cellular plasmid uptake and transient expression due to rapid modification of plasmid DNA by host cells [19, 20].

Table 29.2 Gene therapy delivery vectors

Delivery method	Plasmid	Retrovirus/Lentivirus	Adenovirus	Adeno-associated virus (AAV)	Small molecule
Mode of expression	Transfection and translation	Integration into host genome	Episome formation and translation	Episome formation and translation	Not applicable
Gene transfer	Low potency Low specificity	Low potency Low specificity	High potency Low specificity	Variable potency and specificity	Not applicable
Major advantages	Low toxicity Cost and ease of production	Persistent gene expression Useful for proof-of-concept experiments	High transduction efficiency Low oncogenicity	Low immunogenicity and oncogenicity Highly cardiospecific AAV subtypes	Diverse potential targets (e.g. cell cycle regulators, transcription factors, ion channels)
Major disadvantages	Inefficient, low level of cellular uptake Transient expression	Potential for insertional mutagenesis and tumorigenesis High immunogenicity	Potential immunogenicity (local inflammation and systemic toxicity)	Small cassette size (~5 kB) Neutralizing antibody formation	Transient intracellular concentrations Less well-studied than other methods

Viruses

Viruses used for gene delivery are replication deficient and capable of inserting a transgene of interest relatively efficiently. The type of virus impacts kinetics, specificity, and immune response. **Integrative viruses** (family *Retroviridae*) insert genetic material directly into the host genome for expression by the target cell. **Retroviruses** only integrate into dividing cells such as fibroblasts and are unable to integrate into the genome of quiescent cells such as cardiomyocytes [19, 20]. ***Lentiviruses*** have been utilized more frequently, as these viruses possess proteins for transport across the nuclear membrane which allows integration into non-dividing cells [19, 20]. Integrative viruses, however, are not suited for most clinical uses given that the location of transgene insertion is largely random, potentially resulting in insertional mutagenesis and increasing the risk of malignancy [22].

Adenovirus, a non-integrative DNA virus with many serotypes of varying tropism and pathogenicity, can be used to induce robust but transient (lasting days to weeks) transgene expression [19]. As many serotypes are closely related to human pathogens, a key perceived disadvantage is immunogenicity, resulting in regional inflammation at the target tissue, but this has rarely been seen except for the well-known University of Pennsylvania case of Jesse Gelsinger, who died as a result of a systemic inflammatory response to intravenous delivery of a very high dose of adenovirus vector in the early days of clinical gene therapy trials [23].

Adeno-associated viruses (AAVs) are DNA vectors with no pathogenicity in humans, lower inflammatory response, intermediate persistence of transgene expression, and cardiospecific serotypes [19, 20]. They are limited by host immune response, need for frequent re-dosing, and a small payload capacity of 4.8 kb, compared to 36 kb for adenovirus and ~10 kb for most *Lentivirus* [19, 24]. **Sendai virus** (SeV), a non-integrative RNA virus with direct translation of viral RNA by host ribosomes, has similar properties to AAVs and has been investigated more recently for cardiac regeneration, with early reports suggesting transfection with SeV may be able to achieve more robust transgene expression resulting in faster and more efficient cellular reprogramming [21].

MicroRNA

MicroRNA (miRNA) are non-coding nucleotides which serve an important role in post-transcriptional regulation by binding messenger RNA (mRNA) and preventing translation of target genes [25–27]. In other words, they do not introduce new coding genetic material, but rather impose negative expression of target genes. A viral vector is typically still required for transport and transcription of miRNA. **Small molecules** capable of upregulating cardiogenic genes, downregulating fibrotic signaling or regulating epigenetics have also been reported with a similar efficiency to that of traditional viral vectors in appropriate indications, such as reprogramming [28–30]. There is considerable interest in this strategy due to presumed greater safety and ease of production and administration. The primary limitations include transient expression requiring re-dosing, lack of pharmacokinetics data, study of off-target effects, and the potential for polypharmacy in the clinical setting.

Routes of Administration

Administration of genes, miRNA or small molecules may be achieved systemically or locally via intramyocardial or intracoronary techniques. Intravenous administration would allow the material to arrive at the myocardium through systemic circulation. Although this requires minimal effort and has low procedural risk, target tissue concentration are typically extremely low and carries the potential for relatively high off-target concentrations and effects. Intracoronary injection is a more invasive, but still percutaneous, method of administration directly into the myocardial blood supply that would be expected to produce a more favorable ratio of myocardial to systemic exposure. However, viral vectors do not cross the endothelial membrane efficiently and the high flow rate of systemic blood through the coronary vasculature results in significant 'washout' of therapeutic agent [31, 32]. Additionally, the nature of CAD is such that the myocardial territories most in need of therapy would receive a smaller proportion of agent due to their compromised blood supply.

Target genes may also be delivered locally or **intramyocardially** via direct injection into the infarcted territory, which may be targeted by nuclear medicine perfusion imaging, catheter-based ultrasound, or directly via thoracotomy, as is routinely done in *in vivo* studies and previous gene therapy clinical trials [6, 17]. Direct comparison of intracoronary versus intramyocardial delivery of adenovirus vector demonstrated at least a 33-fold higher concentration of viral vector in target tissues with intramyocardial injection [33]. Angiogenesis trials were more likely to report positive outcomes in patient treated with intramyocardial injection when compared to intracoronary administration [6, 14, 15]. A potential limitation of direct injection is that the area of viral transduction at each injection site is limited and has been reported to be only up to 1–2 cm, albeit with older, less efficient viral vectors and dependent on the injectate volume [34, 35]. The ultimate therapeutic effect size and number of required injections remains an important factor in the translation of success in small animal models to clinical application in humans. In some cases as with secreted angiogenic factors, this volume of distribution may nevertheless be more than adequate for therapeutic effect.

Angiogenesis

The insult which precipitates the complex remodeling in ischemic cardiac disease and resultant heart failure is a mismatch between myocardial demand and coronary supply. Coronary stents and surgical bypass are able to address focal obstruction in named coronary arteries and branches, but patients increasingly present with diffuse disease not amenable to these interventions due to comorbidities, such as diabetes or renal failure, which affect small coronary vessels [36]. Initial attempts at applying genetic therapy to cardiac disease focused on rectifying this deficiency by increasing collateral blood supply via the stimulation of **angiogenesis**, the creation of new branches from existing blood vessels. **Vasculogenesis,** in contrast, refers to the *de novo* formation of new vessels from mesoderm progenitor cells, which occurs during embryogenesis [36].

The most important specific angiogenic mediator is typically considered to be **vascular endothelial growth factor A (VEGF-A)**, which serves as an upstream regulator for the growth, differentiation, and maturation of vascular tissues through other paracrine factors such as **fibroblast growth factors (FGFs)**, angiopoietin, **hepatocyte growth factor (HGH)**, **hypoxia-induced factor alpha (HIF-α)** and **transforming growth factor beta (TGF-β)** [37]. Preclinical evidence demonstrated that genetic therapy to stimulate VEGF transcription, or direct administration of recombinant VEGF, resulted in increased vessel density of cardiac tissue *in vitro* and improvement in myocardial perfusion and/or left ventricular contraction in animal models, clearing the way for clinical trials [14, 15, 36].

Beginning in 1997, numerous clinical trials were conducted to investigate the effect of various combinations of angiogenic factors and delivery techniques in patients with diffuse CAD, with favorable safety outcomes but mixed results regarding clinical efficacy [6, 14, 15]. Generally, VEGF isoforms were the angiogenic factor of choice in these trials, with intracoronary or intramyocardial delivery by recombinant plasmid or viral vector. Functional outcome measures that were employed in these trials include treadmill exercise testing, myocardial perfusion imaging, and cardiac-gated MRI to detect wall motion abnormalities.

Retrospective analysis of these trials noted more favorable functional outcomes for adenovirus-mediated delivery over plasmid based delivery, and intramyocardial over intracoronary administration of angiogenic factors [6, 14, 15]. While such trends were obvious in retrospect, equivocal data from individual trials tempered early enthusiasm for cardiac gene therapy and raised doubts about the viability of an angiogenesis-only approach. In an attempt to rectify these generalizations, several new trials are underway, two utilizing VEGF and two with FGF [38]. The KAT301-trial proposes to administer intramyocardial VEGF-D using catheter-based technology for the treatment of medically refractory angina [38]. Another trial aims to use all three major isoforms of VEGF-A, which will be delivered into the myocardium following thoracotomy. Given the observation that angiogenic gene therapy may lead to a higher benefit in postmenopausal women, the ASPIRE (non-controlled) and AWARE (placebo-controlled) trials also seek to administer intracoronary adenovirus FGF-4 to postmenopausal women and measure the perfusion defects using nuclear imaging [38, 39].

Cardiac Cellular Reprogramming

Following Yamanaka and Takahashi's seminal discovery in 2006 that terminally differentiated cells may be reprogrammed into **induced pluripotent stent cells (iPSCs)** using **Oct4**, **Sox2**, **Klf4**, and **c-Myc**, Ieda et al. in 2010 demonstrated that dermal and cardiac murine fibroblasts can be directly reprogrammed, i.e. bypassing a progenitor or stem cell state, to functional **induced cardiomyocytes (iCMs)** using the defined reprogramming factors **Gata 4**, **Mef2c** and **Tbx5** (GMT) [11, 12]. This approach to cardiac regeneration has been shown to improve post-infarct ejection fraction approximately 10–25% from baseline and reduce fibrosis by nearly 50% in murine models after intramyocardial injection of GMT [23, 25, 40–44]. Parenthetically, the reduction in fibrosis may be a result of newly formed iCMs secreting factors that inhibit collagen expression and matrix metalloproteinase activity, impairing normal fibroblast functions. Investigators have continued to enhance the reprogramming factor cocktail of cardiogenic genes or add supplemental angiogenic, antifibrotic or epigenetic modulating factors to support the nascent iCMs and further increase reprogramming efficiency [5, 16–18] (Fig. 29.1).

Suppressing the native fibroblast signature may be just as important as delivering cardiogenic genes to induce reprogramming. For example, suppression of pro-fibrotic signals such as **Snai1** and **TGF-β** has been shown to greatly increase the efficiency of reprogramming regimens [27, 45, 46]. Inclusion of ALL such procardiogenic and antifibrotic factors (shown in Table 29.1) would, of course, be cumbersome to deliver into cells and likely impractical for clinical use, so it will be important to isolate which factors are most critical [16, 17]. An optimal combination of cardiogenic factors and anti-fibrotic factors may hold the key to clinically relevant reprogramming. Because differentiated cells have intrinsic protective mechanisms which resist loss of cell phenotype, the addition of factors to overcome these epigenetic barriers perpetuating cellular senescence can also reduce the total amount of genetic material which must be delivered [47]. Toward this end, downregulation of select epigenetic regulators, e.g. **Bmi1**, **p63** or chromatin remodeling agents, enhance reprogramming efficiency, even reducing the need for additional reprogramming factors [47–51].

Challenges in Cardiac Gene Therapy

Cardiac gene therapy provides an effective way to deliver new genetic material to the heart and may address many of the challenges of cellular implantation, such as poor electromechanical integration, low cell survival and prohibitively high cost required to procure and implant cells. Nonetheless, several remaining hurdles need to be taken into account prior to clinical use of gene therapy for coronary artery disease.

Pharmacokinetics data regarding gene "dosage" and frequency needed to achieve the desirable effect, novel non-integrative delivery vectors, minimally invasive delivery techniques, and analysis of off-target effects of genes are all concerns that must be addressed prior to clinical application [6, 16, 17].

Challenge specific to angiogenic gene therapy includes overcoming public misconception related to mixed results from previous clinical trials. The aforementioned promising clinical trials, however, may help bring angiogenesis back into the clinical arena [6]. Challenges specific to cardiac cellular reprogramming include human epigenetic constraints to reprogramming, lack of long-term *in vivo* data (>12 weeks), and the need for larger animal, i.e. porcine, studies [5, 16–18]. Given the anticipated lower efficiency of reprogramming in human cells, synergistic therapies such as angiogenic agents, antifibrotic agents, or epigenetic modulators are being investigated.

Conclusion

The application of gene therapy in cardiac disease holds great promise, but is not yet ready for widespread clinical application. However, the great strides in understanding the underlying molecular mechanisms of cardiogenesis over the last two decades have culminated into the current era of cardiac cellular reprogramming. While keeping in mind the lessons learned from initial clinical investigations in this arena, there is optimism that a new wave of clinical trials utilizing these tools may prove useful for millions of patients suffering from chronic coronary artery disease worldwide.

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Combined Carotid and Coronary Artery Disease

30

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High Yield Facts

- An association between coronary and carotid artery disease is well known. About 7% patients referred for coronary artery bypass grafting (CABG) have severe asymptomatic carotid artery stenosis. With severe stenosis, almost ½ also have bilateral involvement.
- Duplex carotid ultrasound is an excellent screening tool to assess the status of the carotid arteries. Selective screening of high-risk patients is recommended as that leads to a better cost-benefit ratio.
- Various options exist for the management of these patients; choice is dictated by patient presentation, acuity of carotid and coronary symptoms and institutional protocol.
- Symptomatic carotid stenosis or severe bilateral stenosis warrant carotid endarterectomy, either as a staged procedure or concomitantly with coronary artery bypass surgery.
- Concomitant surgery allows resolution of carotid stenosis prior to cardiopulmonary bypass for CABG. Benefits are shortened hospital stay and lower overall costs. Concern remains long procedural duration. Recent data demonstrates that results are non-inferior to staged procedures.
- In the presence of stable coronary artery disease and critical symptomatic carotid stenosis, the traditional option remains carotid endarterectomy (CEA) followed by CABG. However, inter-stage myocardial infarction remains an issue with this approach.
- Isolated CABG is recommended for patients with asymptomatic carotid artery stenosis.
- Preliminary data demonstrates that carotid stenting is as safe as carotid endarterectomy and appears an attractive minimally invasive approach. However, need for aggressive antiplatelet therapy remains a cause for concern when combined with CABG as a synchronous procedure.

Introduction

Atherosclerosis is a generalized disorder often involving multiple vascular systems [1]. Stroke after cardiac surgery can be devastating. Thus, many cardiac surgical centers preoperatively screen patients for concomitant carotid lesions prior to coronary artery bypass grafting (CABG) [2, 3]. Carotid ultrasound is the accepted modality for initial noninvasive testing for carotid artery stenosis.

However, guidelines regarding screening as well as clinical management of asymptomatic carotid stenosis in patients scheduled for CABG are based on limited data [4–6]. This chapter presents an overview of current trends and a rational approach to this clinical problem.

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Should Routine Carotid Artery Screening Be Performed Prior to Surgery?

Co-existent carotid artery stenosis was reported in 14% patients scheduled for CABG at the Cleveland Clinic [7]; among these, ½ had severe stenosis (bilateral 60–80% or unilateral 80–100%). Fukuda et al. [8] report that only 4% of their patients underwent carotid revascularization due to lesions found during asymptomatic screening. Stroke occurrence was not related to screening; in fact, no patient with stenosis >50% suffered stroke. Salehiorman et al. [9] report no causal relationship to carotid stenosis and ipsilateral stroke.

A review of literature demonstrates very low yield with non-selective carotid artery screening at the time of CABG. We recommend selective screening for the following patients: history of diabetes, hypertension, peripheral arterial disease, history of transient ischemic attack/stroke, carotid bruit on exam, amaurosis fugax or new onset extremity weakness and left main coronary artery disease [4].

Management of Concomitant Carotid and Coronary Artery Disease

Management options for co-existent carotid and coronary artery disease include:

- Combined CABG + carotid endarterectomy (CEA)
- Staged approach: either CABG followed by CEA or CEA followed by CABG
- Carotid artery stenting followed by CABG
- Off-pump CABG with/without CEA

Combined Carotid Endarterectomy and Coronary Artery Bypass Grafting

The combined approach consists of CEA followed by CABG in the same anesthesia setting. This approach is selected in patients with symptoms which can be directly associated to the carotid lesion or with significant bilateral disease. It is an option when patients present with acute coronary syndrome, left main disease or an unfavorable coronary anatomy where CABG cannot be delayed.

Gopaldas et al. [10] report comparable stroke and early mortality when comparing the synchronous and staged approaches. However, a combined approach led to a significant reduction in cost as well as hospital stay. Shishehbor et al. [11] report a comparable peri-operative stroke rate when comparing staged versus combined procedures. Rates of peri-operative MI were much lower with the combined approach rather than CEA-CABG (0.5% vs 24%). A meta-analysis pooling 12 studies reported comparable results in both staged and synchronous cohorts pooled [12].

However, this approach should be implemented with caution in patients with asymptomatic disease. A recent trial [13] demonstrates that the 30-day composite end-point of death/stroke was higher (18% vs 9%) in patients undergoing combined vs isolated CABG respectively.

Thus, we would recommend a combined approach only in symptomatic patients who need urgent/semi-elective CABG.

Staged Carotid Endarterectomy and Coronary Artery Bypass Grafting

The traditional staged approach of prior carotid endarterectomy followed by CABG is reserved for patients who present with stable coronary artery disease. The main concern of this approach remains inter-stage myocardial infarction [11]. An extensive meta-analysis [14] reported that the risk of operative stroke was lowest (2.7%) when a staged CEA-CABG procedure was conducted. However, as reported subsequently by Shishehbor et al. [11], this benefit was reduced given the increased risk of myocardial infarction.

Hence, we would recommend this approach when treating patients with chronic stable angina and a good myocardial reserve. An expert anesthesia and critical care team may help to reduce the concerns with this approach. We would also recommend this approach for patients with symptomatic carotid disease and clinical history which correlates to this lesion.

Role of Carotid Artery Stenting

Results of the ACT I trial (Asymptomatic Carotid Trial I) and CREST trial (Carotid Revascularization Endarterectomy Versus Stenting Trial) report comparable event rates of death, stroke and myocardial infarction between carotid endarterectomy and carotid artery stenting (CAS) [15, 16]. Thus, carotid artery stenting has emerged as a more minimally invasive alternative to CEA [17].

A large cross-sectional study in the US reported reduced rates of in-hospital stroke for synchronous CAS/CABG as compared to CEA-CABG [18]. Shishehbor et al. report better 1-year survival for patients for patients undergoing CAS as compared to CEA [11].

However, the need for aggressive anti-platelet therapy after CAS is an important consideration which may delay CABG. Individual expertise, availability of embolic protection devices and institutional protocol should be considered when choosing between CAS and CEA either as a staged procedure or concomitantly with CABG.

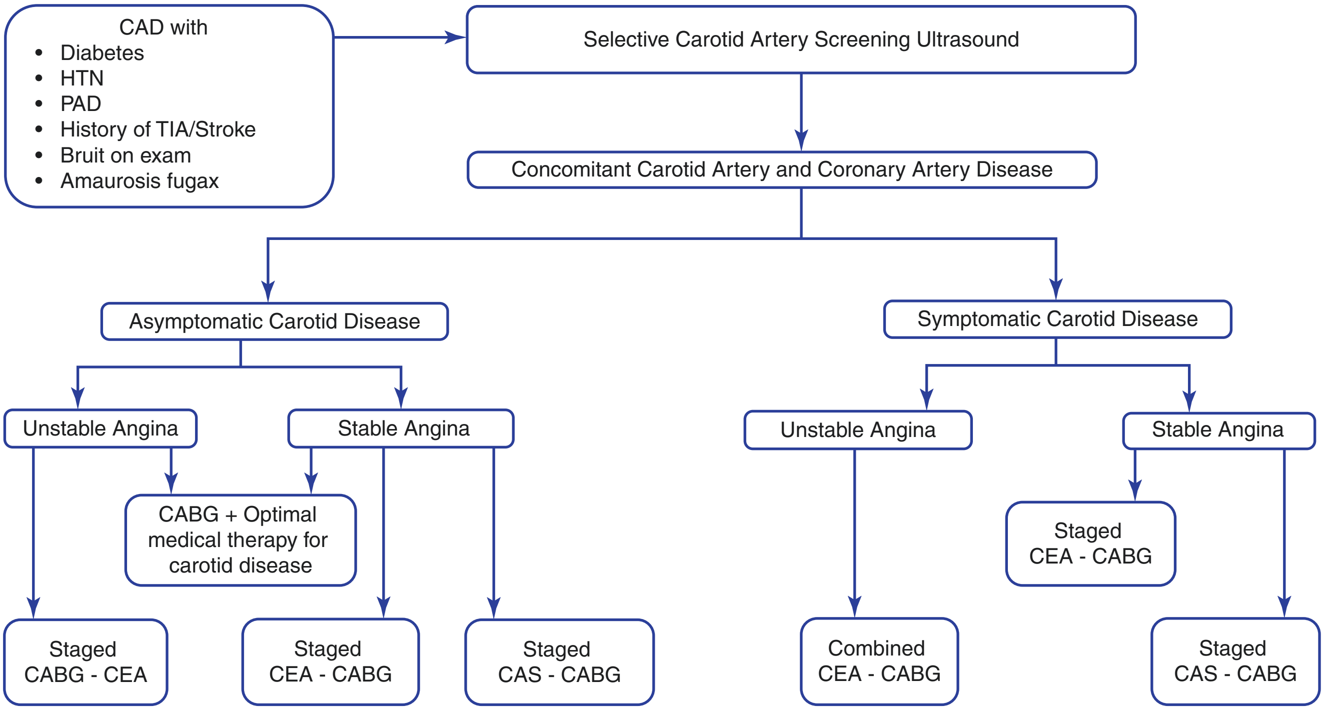
CAD with
• Diabetes
• HTN
• PAD
• History of TIA/Stroke
• Bruit on exam
• Amaurosis fugax
Selective Carotid Artery Screening Ultrasound
Concomitant Carotid Artery and Coronary Artery Disease
Asymptomatic Carotid Disease
Symptomatic Carotid Disease
Unstable Angina
Stable Angina
CABG + Optimal medical therapy for carotid disease
Staged CABG - CEA
Staged CEA - CABG
Staged CAS - CABG
Unstable Angina
Stable Angina
Staged CEA - CABG
Combined CEA - CABG
Staged CAS - CABG

Fig. 30.1 A practical approach to patients with combined coronary and carotid artery disease. (Adapted with permission from Poi MJ, Echeverria A, Lin PH. Contemporary management of patients with concomitant coronary and carotid artery disease. World J Surg 2018;42:272–282.) *CABG* coronary artery bypass grafting, *CAD* coronary artery disease, *CAS* carotid artery stenting, *CEA* carotid endarterectomy, *HTN* hypertension, *PAD* peripheral arterial disease, *TIA* transient ischemic attack

Figure 30.1 illustrates a practical approach towards procedural selection. As stated previously, apart from patient presentation, operator skill and comfort, institutional protocol and preferences play an important part in selecting the appropriate pathway. However, stroke is devastating; for the patient and morale of the care-givers. Hence, we should adopt all means available to reduce the incidence of this catastrophic complication in our patients.

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Coronary Artery Aneurysms and Fistulas

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and William Jeremy Mahlow

High Yield Facts

- Coronary artery aneurysms are defined as the local dilatation of the artery greater than 1.5-times that of the diameter of the adjacent segments, and can be very large, termed "giant aneurysms".
- Coronary angiography is the gold standard for diagnosis of coronary artery aneurysms and fistulas.
- Treatment of aneurysms consists of medical therapy, covered stents, and surgical intervention.
- Large fistulas require treatment, regardless of symptoms.
- For small to moderate fistulas, symptoms guide timing of intervention.
- Surgical ligation and transcatheter closure are well-established techniques for closure of coronary fistulas.

Coronary Artery Aneurysms

Introduction

Coronary artery aneurysms or ectasia are present in 0.3–4.7% of the population and are defined as a dilatation of a localized segment of the artery greater than 1.5-times that of the diameter of the adjacent segments [1, 2]. In more rare circumstances, coronary dilatation can be much more significant and reach up to four times the adjacent coronary segment, termed "giant coronary artery aneurysms". The prevalence of giant coronary aneurysms in the general population is 0.02–0.2% [3]. Aneurysmal formation is most commonly seen in the right coronary artery (40–87%), and less commonly in the left system. Multi-vessel aneurysms and left main artery aneurysms are very rare [2–5]. Saphenous vein grafts can also develop aneurysmal portions. Males are three times more commonly affected than females [1, 2, 4].

Classification

Coronary artery aneurysms are classified as small, medium and large based upon the luminal diameter, usually described based on coronary angiography (Table 31.1). There are four types determined by the extent of vessel involvement (Table 31.2). Saccular aneurysms occur when the maximal transverse diameter overcomes the longitudinal diameter. In contrast, fusiform aneurysms are defined by the longitudinal diameter exceeding the transverse diameter [1, 3, 6, 7].

Determining the extent of vessel wall involvement is important from a treatment perspective. True aneurysms involve all three layers of the vessel wall (tunica intima, tunica media, tunica adventitia), whereas false, or "pseudoaneurysms", only involve the outer layers. Coronary angiog-

Table 31.1 Size classification of coronary aneurysms

Size	Luminal diameter
Small	<5 mm
Medium	5–8 mm
Giant	No widely accepted definition

Table 31.2 Type classification of coronary aneurysms

Type I	Diffuse ectasia in two or three vessels
Type II	Diffuse ectasia in one vessel with localized aneurysmal formation in a second vessel
Type III	Diffuse ectasia limited to one vessel
Type IV	Localized/segmental ectasia

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raphy is a “luminogram” and does not allow for information regarding the vessel wall involvement. Intravascular ultrasound or other imaging modalities are required [8, 9].

Risk Factors and Associations

Male gender and hyperlipidemia are the only independent risk factors found to be significantly related to aneurysmal formation of the coronary arteries. Obstructive coronary artery disease is common in patients with coronary artery aneurysms; about 71% of patients in a study by Baman illustrated the co-existence of the two diseases [2, 10]. There are stronger associations between lipid disorders and ectasia with relation to lower HDL levels and high LDL/HDL ratios [11]. Coronary artery ectasia has also been discussed in relation to connective tissue disorders, infections (syphilis, Lyme disease, HIV), congenital heart disease, and vasculitis (Takayasu arteritis, Kawasaki disease) [11, 12]. Iatrogenic causes have been described with relation to coronary intervention procedures [3, 4].

Pathogenesis

Several mechanisms are thought to contribute to the formation of coronary artery aneurysms. In all cases, there is disruption of the vessel wall, leading to dilation of the vessel. Given the significant association of ectasia with coronary artery stenosis, it is hypothesized that plaque formation leading to changes in the flow hemodynamics and shear stress in the surrounding vessel can contribute to aneurysm formation [6, 13, 14]. Lipoprotein formation in the vessel wall contributes to this plaque and subsequent inflammatory reaction [6, 11].

A variety of inflammatory molecules play a part in the enzymatic degradation in the vessel wall leading to dilation (Fig. 31.1). Adhesion molecules, C-reactive protein, vascular endothelial growth factor (VEGF) and leukotrienes are inflammatory molecules and are all found in elevated concentration in coronary artery disease and coronary artery aneurysms [6, 15–18]. Increased levels of angiotensin II are also associated with coronary artery aneurysms and increase vessel inflammation and endothelial dysfunction specifically via the interleukin-6 pathway [19, 20]. Elevated homocysteine levels and insulin levels contribute to alterations in the vessel wall as well [6, 21–23].

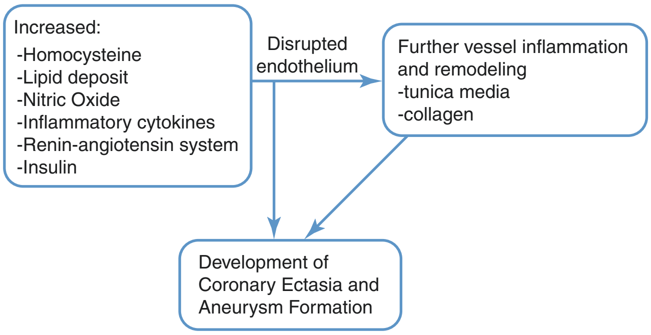

Fig. 31.1 Pathogenesis of coronary aneurysms. Figure adapted from [6]

Clinical Presentation

A great majority of coronary artery aneurysms are incidentally discovered on coronary imaging. Anginal symptoms, with or without myocardial infarction, as well as dyspnea are amongst the most common symptoms [12]. Rupture is rare, however, but when it occurs, sudden death, tamponade, and acute heart failure are possible outcomes of this unfortunate event [3]. A mediastinal mass may also be seen on imaging [24]. The degree of symptoms may also be related to the amount of surrounding coronary artery stenosis or thrombus causing flow changes in the vessel [12]. Distal embolization has also been observed. Fistula formation between aneurysm and other cardiac chambers has been described, and shunts may be present [15, 25].

Diagnosis

The gold standard for diagnosis is coronary angiography (Fig. 31.2), although coronary CT angiography can be useful as well (Figs. 31.3, 31.4, 31.5, 31.6 and 31.7), particularly in cases with other associated anomalies, such as fistula formation [8].

Treatment

The use of optimal medical therapy in patients found to have atherosclerotic disease is strongly recommended, specifically aspirin and statin therapy [10, 26]. The addition of angiotension converting enzyme inhibitor for its anti-inflammatory properties is recommended; however, controlled trial data evaluating the benefit of these medications specifically in aneurysmal coronary disease is lacking [10, 25].

Although medical therapy is recommended for all aneurysmal coronary disease, percutaneous or surgical treatment is not indicated for asymptomatic small- or medium-sized aneurysms [27]. However, large aneurysms may require an invasive approach, particularly when they are associated with symptoms or evidence of myocardial ischemia. Aneurysms which are three to four times the size of the native vessel (giant aneurysms) have a higher rate of rupture,

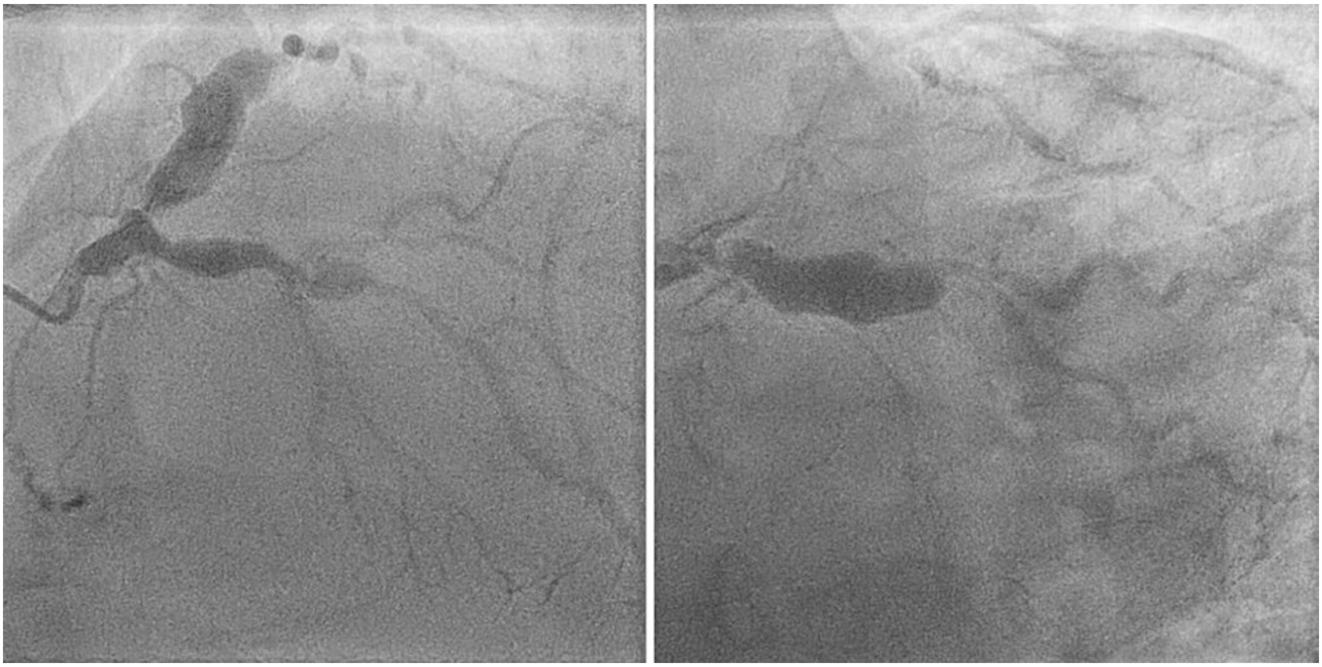

Fig. 31.2 Coronary angiography illustrating coronary artery aneurysms

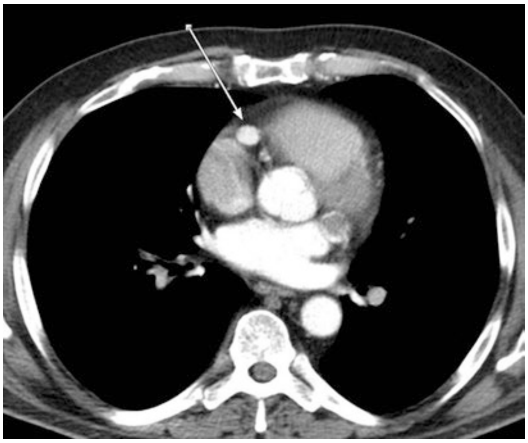

Fig. 31.3 Coronary CT angiography revealing 1.3 cm aneurysm of the proximal to mid portion of the right coronary artery (arrow)

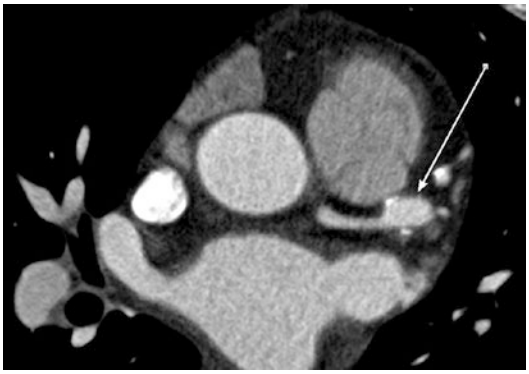

Fig. 31.4 Coronary CT angiography demonstrating aneurysm at the left circumflex ostium and proximal portion of the artery (arrow)

and surgery is generally recommended [28]. Prior to embarking on an invasive strategy, a team approach that involves a joint decision with a cardiac surgeon and an interventionalist should be considered [12]. The best strategy may be to individualize the approach for each patient based on the etiology, size of aneurysm, symptoms and comorbidities. If the patient is not suitable for surgical therapy, the mainstay of percutaneous therapy consists of covered stents [12, 29]. This approach carries a significant risk of branch occlusion, restenosis and thrombosis well as the necessity of antiplatelet therapy [12, 29]. There have also been reports of utilizing coil embolization, but this technique is only recommended with very experienced operators [30].

Although the different surgical techniques have not been studied in detail, the literature does contain reported cases of proximal ligation, aneurysmectomy and revascularization. Kumar et al. [31] published a case series of three patients who underwent this surgical revascularization technique with excellent results. However, surgical therapy must be individualized based on the anatomy and etiology of the aneurysms.

Coronary Artery Fistulas

Introduction

Coronary artery fistulas (CAF) are abnormal connections between the coronary arteries and any of the cardiac chambers (Cameral fistulas) or other vessels. They are also known

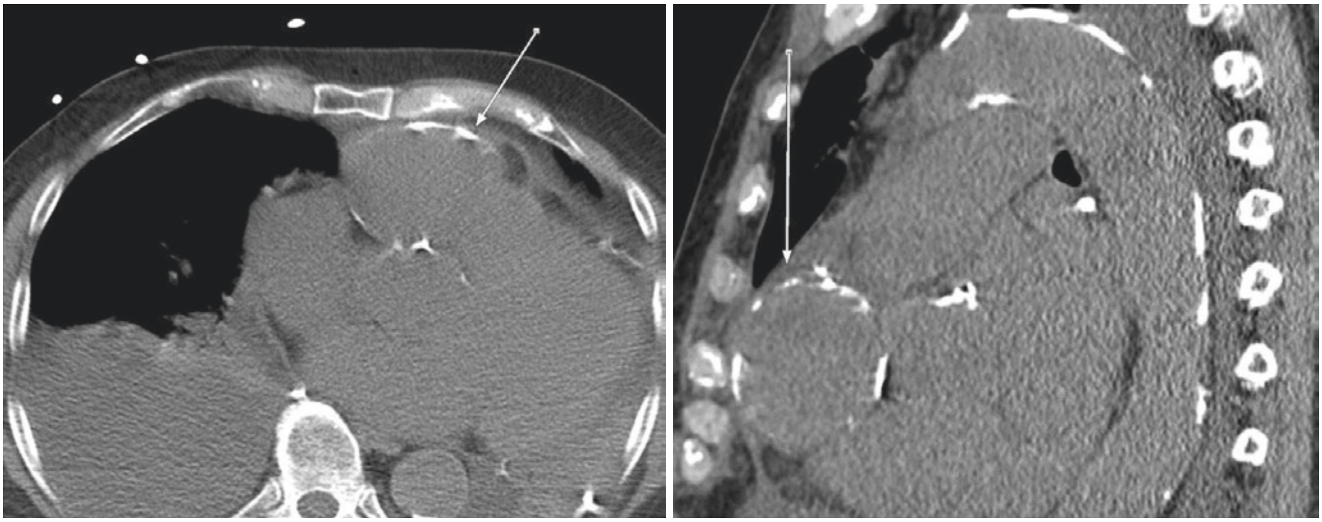

Fig. 31.5 Giant aneurysm (6.7 cm) of a coronary artery bypass graft (arrow)

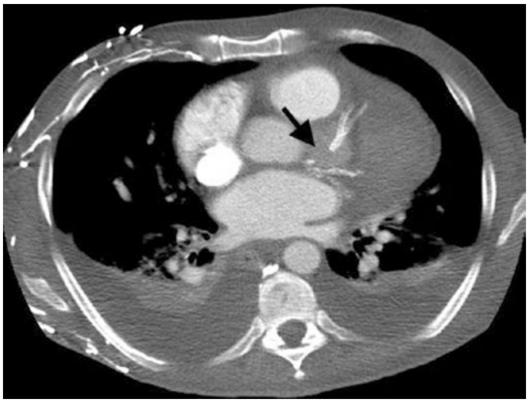

Fig. 31.6 Contrast enhanced CT demonstrating a giant coronary aneurysm originating from the distal left main artery or proximal left anterior descending artery (arrow)

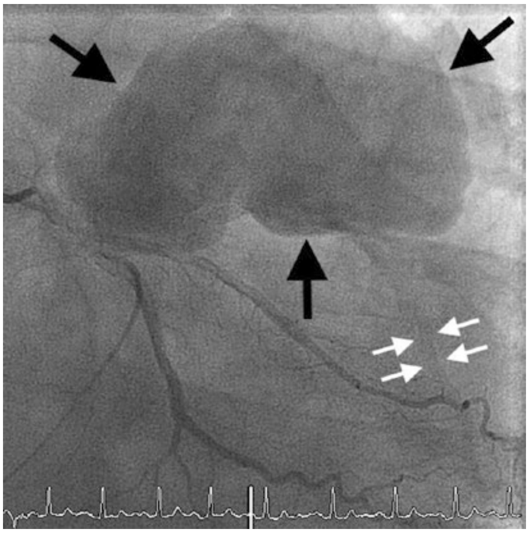

Fig. 31.7 Coronary angiogram of the same giant coronary artery aneurysm seen in Fig. 31.6 (measuring 70 × 40-mm in this view). The distal left anterior descending artery is only partially filled with contrast (white arrows)

Table 31.3 Angiographic classification of coronary artery fistulas[a]

Type A (proximal type)	Proximal coronary segment dilated to the origin of fistula with normal distal end
Type B (distal type)	Coronary dilated over entire length, terminating as a fistula mainly in the right side of the heart (end-artery type), coronary proximal to the fistula may have regular branches

[a] From Sakakibara et al. [36]

as coronary arteriovenous fistulas (CAVF). CAF are often due to abnormal embryological development but may be acquired from invasive surgical procedures, trauma, infection and Kawasaki disease [32–34].

Classification

Nomenclature of CAF relies on a descriptive analysis of the vessel of origin and its termination [35]. One angiographic classification has been proposed by Sakakibara and associates [36] (Table 31.3).

Epidemiology

Coronary anomalies are estimated to occur in 0.2–1.2% of the population with CAF present in 0.002% of the general population [35]. CAF represent 13% of all the anomalies of the coronary arteries and are visualized in 0.18% of those undergoing coronary angiography [37]. The prevalence of CAF on coronary CT angiography has been shown to be as high as 0.9% [38]. CAF are isolated in 55–80% of cases and are associated with congenital disease in 20–45% of cases [39–42]. Associated anomalies include atrial septal defect, patent ductus arteriosus, tetralogy of Fallot, pulmonary atresia with intact ventricular septum, and coronary

Table 31.4 Rate of occurrence of coronary artery fistulas (CAF) from each coronary artery[a]

Major sites of CAF origin	Rate of occurrence (%)
Right coronary artery	50–60%
Left anterior descending artery	25–42%
Left circumflex artery	18.3%
Both coronary arteries	5%
Diagonal	1.9%
Marginal	0.7%

[a]Adapted from Dodge-Khatami et al. [35]

Table 31.5 Incidence of fistula drainage sites[a]

Major termination sites	Rate of occurrence (%)
Right ventricle	14–40%
Right atrium	19–26%
Pulmonary arteries	15–43%
Superior vena cava	1%
Coronary sinus	7%
Left atrium	5–6%
Left ventricle	2–19%

[a]Adapted from Dodge-Khatami et al. [35]

artery disease. Coronary artery disease is seen in 35% of cases [43, 44]. Single fistulas are more common, with multiple fistulas occurring 10.7–16% of the time [45–47] and both coronary arteries involved in 5% of cases [47–49] (Tables 31.4 and 31.5).

Pathophysiology

Most CAF are small and asymptomatic [32]. Pathology primarily occurs through coronary steal and volume overload from shunt physiology. Coronary steal results from compromised myocardial perfusion distal to the fistula as blood will flow through the lower-resistance fistula rather than the smaller and higher resistance myocardial vessels. Shunt physiology and resulting volume overload depend on the fistula flow and the site of termination with resulting left-to-right or left-to-left shunting. Flow through the fistula is dependent upon vessel resistance and the difference in pressure between the coronary artery and the terminating cardiac chamber or vessel.

"Left-to-right" CAF flow to the right heart chambers or venous structures occurs throughout the cardiac cycle similar to a patent ductus arteriosus (PDA) [50] and can result in coronary steal with complications of volume overload of both ventricles and other cardiac chambers [51].

"Left-to-left" CAF flow into the left atrium or pulmonary vein will cause continuous flow throughout the cardiac cycle and volume overload the left chambers only. CAF flow into the left ventricle will cause volume overload of the left ventricle with hemodynamics mimicking aortic valve regurgitation [51].

Clinical Presentation

Most CAFs are small and asymptomatic as myocardial perfusion is not compromised [50]. Untreated CAFs are symptomatic in 19% of patients under 20 years of age and in 63% of older patients [41]. Dyspnea with exertion is the most common symptom [52] and physical exam may reveal a continuous murmur audible at the left lower sternal border [50].

Natural History

Small CAFs in children tend to grow with age [50]. Spontaneous thrombosis and fistula closure is rare and occurs in 1–2% of cases [53]. Complications include volume overload of cardiac chambers, congestive heart failure, arrhythmias, dilation of coronary artery branches proximal to the fistula site, myocardial ischemia and infarction, cardiomyopathy, aneurysm formation from high flow, valvular regurgitation from papillary dysfunction, endocarditis, pulmonary hypertension, and rarely rupture [50, 52, 54–62].

Diagnosis

Coronary angiography remains the gold standard for definitively identifying and planning management of CAFs, although less invasive imaging techniques are becoming more common [63–66]. Electrocardiogram may indicate chamber enlargement, atrial fibrillation or ischemia, while chest X-ray may show cardiomegaly and pulmonary congestion. Transthoracic echocardiography or transesophageal echocardiography (TEE) can diagnose CAF and occasionally show the origin and termination of the anomaly (Fig. 31.8). These modalities are also useful for detecting sequela such as chamber enlargement, volume overload and wall motion abnormalities [67–70]. Computed tomography (CT) cardiac coronary angiography and magnetic resonance imaging (MRI) are becoming more common as accurate and noninvasive imaging modalities for detection of major CAFs and other coronary artery anomalies. As coronary angiography remains the gold standard, invasive modalities such as intravascular ultrasound (IVUS), fractional flow reserve (FFR) and instant wave-free ratio (iFR) are further able to demonstrate anatomy and hemodynamics [71].

Management Guidelines

The 2008 ACC/AHA Guidelines for the Management of Adults with Congenital Heart Disease recommend that a large CAVF, regardless of symptomatology, should be closed after the fistula's course is defined. The guidelines also recommend that small to moderate CAVF be closed in the presence of symptoms including myocardial ischemia, otherwise unexplained systolic or diastolic dysfunction or enlargement, endarteritis or arrhythmia

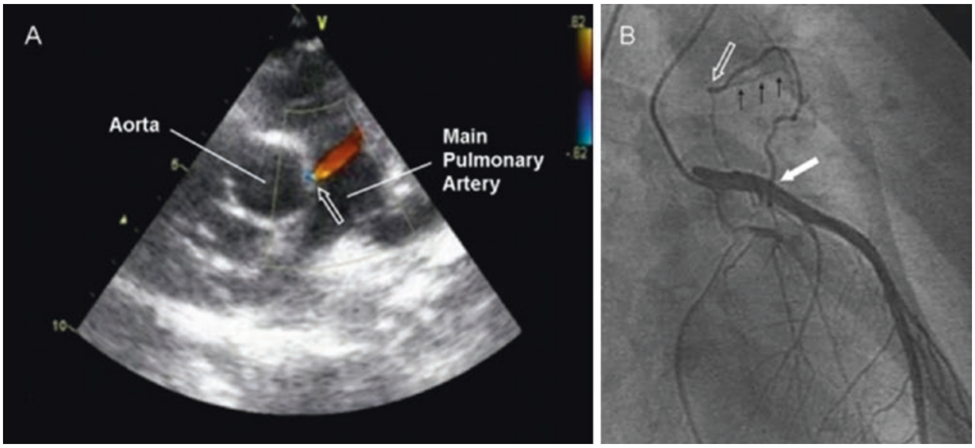

Fig. 31.8 (**a**) Transthoracic color Doppler echocardiogram shows a continuous flow in the high parasternal short axis view, originating from a small entry site on the wall of the main pulmonary artery (arrow). (**b**) A selective left coronary angiography in the same patient shows a fistula connecting the proximal portion of the left anterior descending coronary artery (solid large white arrow) with the main pulmonary artery (clear arrow). The small three white arrows indicate drainage into the pulmonary circulation. (Reproduced from Quantrini I, et al. Cardiovasc Ultrasound 2007;5:19. Open Access article)

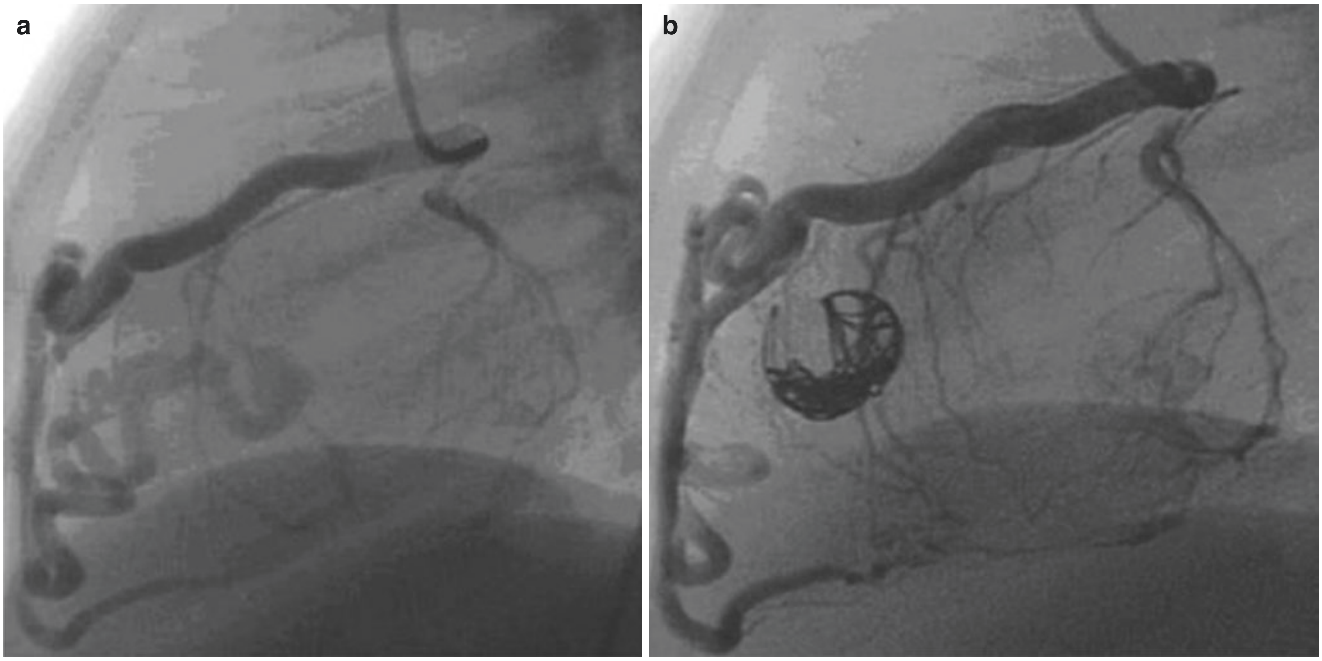

Fig. 31.9 (**a**) A very tortuous fistula between the left anterior descending coronary artery and the right ventricle. (**b**) The fistula is closed by controlled-release coils

(Class I, Level of Evidence: C) [72]. Patients with small, asymptomatic CAVF should not undergo treatment (Class III, Level of Evidence: C). In these patients clinical follow-up with echocardiography every 3–5 years can be useful to exclude development of symptoms or complications that may alter management.

Treatment

Treatment options for CAF are either surgical ligation or transcatheter closure. Surgical ligation can occur alone with or without cardiopulmonary bypass or with coronary artery bypass grafting [32]. Surgical methods have low morbidity and mortality with most patients remaining asymptomatic at long-term follow up [40–73].

Transcatheter closure during cardiac catheterization is becoming more common with devices including various occlusion coils (Fig. 31.9), detachable balloons, covered stents, double umbrellas, vascular plugs, and polyvinyl alcohol foam. Risks of these devices include distal embolization, dissection, and myocardial infarction.

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Part III

Valvular Heart Disease

32

Mechanical Prosthetic Valves

Matthew C. Henn and Marc R. Moon

High Yield Facts

- Mechanical valves remain the most durable option for valve replacement with most new generation valves reporting 0% structural failures with follow-up of >10 years.
- Based on current guidelines in North America and Europe, mechanical valves are recommended in patients <50 years old who can tolerate anticoagulation and should be considered in patients between 50 and 65 years old after a discussion of the risks and benefits.
- Valve thrombosis risk remains low (<1%) for available mechanical valves in both the aortic and mitral positions.
- Current research is focused on lowering the International Normalized Ratio (INR) goal for current mechanical valves and recently the guidelines have been updated to suggest lowering the INR goal for the On-X valve to 1.5–2.0 is reasonable in patients with low risk after 3 months of standard anticoagulation.

Introduction

Valvular heart disease remains a significant healthcare burden worldwide due to the wide range of etiologies of valve disease ranging from congenital malformations, rheumatic heart disease, and degenerative disease [1, 2]. With the aging population, huge burden of rheumatic heart disease worldwide, and dismal outcomes with medical management, there are over 300,000 valve replacements performed worldwide [1, 3–7]. It is estimated that the number of patients requiring valve replacement worldwide will triple by 2050 [3, 4, 6, 8].

The first mechanical valve implant was performed in the 1950s in which a mechanical ball-and-cage valve called the Hufnagel Valve was placed in the descending aorta. Multiple other ball-and-cage valves were subsequently designed including the Harken Soroff Valve, which was the first to be placed in the aortic annular position. The first FDA approved valve was the ball-and-cage Starr-Edwards Valve placed in a sub-coronary position [9–11]. It became clear that the ball-and-cage valves, while durable, did not have favorable hemodynamics secondary to turbulent flow. As a result, second generation mechanical valves like the Bjork-Shiley tilting disk valve were produced in the late 1960s to provide more central flow. During the same time period, in an effort to reduce anticoagulation-related complications, bioprosthetic valves and the Ross procedure were developed as alternatives to mechanical valves. Finally in 1977, the St. Jude Medical valve was the first bileaflet prosthesis that ushered in the modern era of mechanical valves (Fig. 32.1). Bileaflet valves allow for increased effective orifice area, improved hemodynamics, and lower profile allowing for easier implantation [11–14].

While mechanical valve technology has improved immensely and the ability to implant them safely has been established, their main shortcoming is the risk of thromboembolism necessitating life-long anticoagulation. Further, with the increasing popularity of bioprosthetic valves owing to their lack of anticoagulation requirement and the advent and increasing acceptance of transcatheter valve replacement, the use of mechanical valve replacement has been declining in recent years [3, 15]. Despite this, mechanical valves remain appealing in certain populations, particularly younger patients because of their supreme durability.

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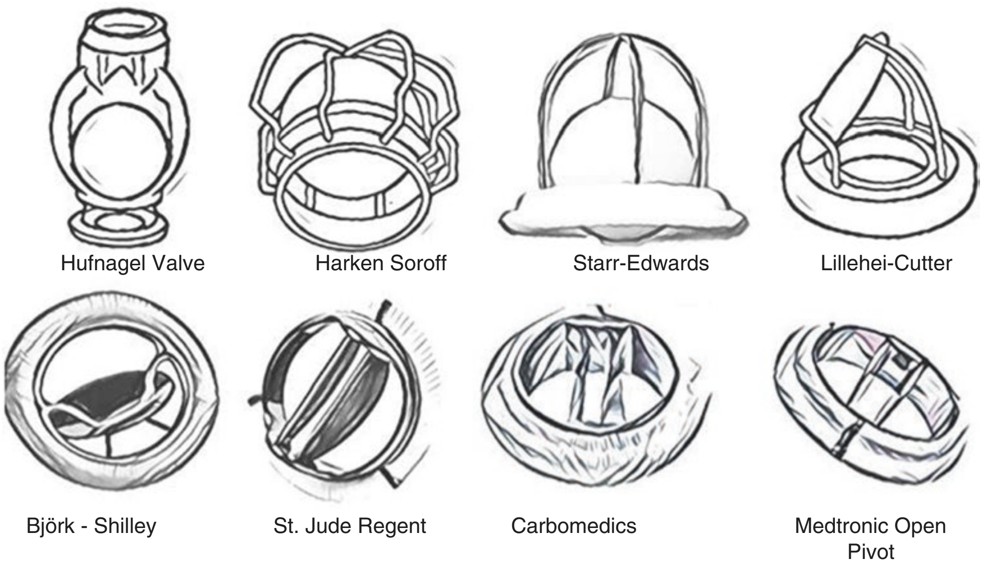

Fig. 32.1 Evolution of mechanical prostheses: Progression of mechanical valve evolution from ball-and-cage valves such as the Hufnagel and Starr-Edwards valves through tilting disk valves to the current bileaflet prostheses. (Reproduced with permission from Russo et al. Cardiovascular Medicine. 2017;20(12):285–292 [11])

Current Indications and Patient Selection

The current North American (AHA/ACC) and European (ESC/EACTS) guidelines for evaluation and selection of prosthetic valves are based on the risk/benefit profile of mechanical and bioprosthetic valves. For younger patients who do not have a contraindication to therapeutic anticoagulation and are willing to have lifelong anticoagulation, mechanical valves are recommended because of their durability and lower likelihood of degeneration requiring re-operation. Conversely, older patients who have a lower life expectancy and higher risk for anticoagulation complications are ideal candidates for bioprosthetic valve replacement. When selecting a valve it is always important to take into account other factors including medication compliance, access to care, and patient characteristics including other indications for anticoagulation, details that would make re-operation more difficult (i.e. porcelain aorta, small root, etc.), and most importantly patient preference (Table 32.1) [16].

Valve selection recommendations have evolved to account for transcatheter valve replacement as an option for reintervention. The ability to place a transcatheter valve inside a degenerated bioprostheses (valve-in-valve) and the improving durability of bioprosthetic valves have led to the reduction in the recommended age limit for mechanical valves from 60 to 50 in North America [16].

Table 32.1 Factors used for shared decision making about choice of valve prosthesis

Favor mechanical prosthesis	Favor bioprosthesis
Age < 50 years	Age > 70 years
• Increased incidence of structural deterioration with bioprosthesis (15-years risk: 30% for age 40 years, 50% for age 20 years)	• Low incidence of structural deterioration (15-years risk: <10% for age > 70 years)
• Lower risk of anticoagulation complications	• Higher risk of anticoagulation complications
Patient preference (avoid risk of reintervention)	Patient preference (avoid risk and inconvenience of anticoagulation and absence of valve sounds)
Low risk of long-term anticoagulation	High risk of long-term anticoagulation
Compliant patient with either home monitoring or close access to INR monitoring	Limited access to medical care or inability to regulate VKA
Other indication for long-term anticoagulation (e.g., AF)	Access to surgical centers with low reoperation mortality rate
High-risk reintervention (e.g., porcelain aorta, prior radiation therapy)	
Small aortic root size for AVR (may preclude valve-in-valve procedure in future)	

AF atrial fibrillation, *AVR* aortic valve replacement, *INR* International Normalized Ratio, *VKA* vitamin K antagonist (Reproduced with permission from Nishamura et al. J Am Coll Cardiol. 2017 Jul 11;70(2):252–289)

Table 32.2 Mechanical prosthesis guidelines

ESC/EACTS guidelines [17]	Class/level of evidence	ACC/AHA guidelines [16]	Class/level of evidence
Valve selection			
Mechanical valve recommended if desired by patient and no contraindications to anticoagulation or the patient is at risk of accelerated structural valve deterioration	I/C	Choice of prosthetic valve should be shared decision that accounts for patient's preferences and includes discussion of anticoagulation and risk of reintervention	I/C-LD
Mechanical valve should be considered if <60 years old for the aortic position and <65 years old for the mitral position	IIa/C	An aortic or mitral mechanical prosthesis is reasonable if patients <50 years old and do not have contraindication to anticoagulation	IIa/B-NR
Bioprosthetic or mechanical valves are acceptable in patients 60–65 years old receiving an aortic prosthesis and 65–70 years old receiving mitral prosthesis, and the choice requires consideration of other factors	IIa/C	It is reasonable for individualized choice of either mechanical or bioprostheses based on individual patient factors and preferences for patients between 50 and 70 years old	IIa/B-NR
Bioprosthetic valve should be considered in patients >65 years old for aortic prosthesis and > 70 years old for mitral prosthesis	IIa/C	Bioprosthetic valve is reasonable in patients >70 years old	IIa/B
Anticoagulation			
Lifelong anticoagulation using vitamin K antagonists is recommended	I/B	Anticoagulation with vitamin K antagonists with INR monitoring is recommended	I/A
The addition of low-dose aspirin may be considered after thromboembolism or concomitant atherosclerotic disease	IIa/C	Aspirin is recommended in addition to vitamin K antagonists	I/A
Median INR goal of 2.5 is recommended in patients with low risk prosthesis[a] and no risk factors for thromboembolism and >3.0 for those with ≥1 risk factor[b]	N/A	Those with mechanical AVR: INR goal of >2.5 is recommended in patients with no risk factors for thromboembolism and >3.0 for those with risk factors	I/B
Those with mechanical MVR: INR goal of >3.0	N/A	A lower INR target of 1.5–2.0 may be reasonable for patients with On-X AVR and no risk factors	IIb/B-R
		Those with mechanical MVR: INR goal of >3.0	I/B

[a] Carbomedics, Medtronic Hall, ATS, St. Jude, On-X, and LivaNova Bicarbon

[b] Mitral or tricuspid replacement, previous thromboembolism, atrial fibrillation, mitral stenosis, or LVEF <35%

These same guidelines state that for patients between the ages of 50–70 it is reasonable to individualize the decision between mechanical and bioprosthetic valve after a full discussion of the tradeoffs of durability (and the need for reintervention), bleeding, and thromboembolism [16]. However, most institutions including ours would not offer mechanical valve replacement to anyone over the age of 65. When comparing the North American guidelines to the European guidelines, the major difference is the age cutoff for mechanical valve recommendation. European guidelines state that mechanical valve should be considered in patients <60 years old for the aortic position and <65 years old for the mitral position while the North American guidelines recommend mechanical valves in both the aortic and mitral positions for those patients <50 years old. The current European and North American guidelines are presented summarized in Table 32.2 [16–18].

While the guidelines do not differentiate between mitral and aortic valve prostheses, there is some evidence that outcomes with mechanical valve replacement differ depending on location of valve. The landmark study of Goldstone et al. found that there was a mortality benefit associated with mechanical mitral valve replacement over bioprostheses that persisted until 70 years of age, but only to age 55 in patients with mechanical aortic valve prostheses [7].

Current Mechanical Valves

Most available valves on the market for both the aortic and mitral position are bileaflet valves composed of pyrolytic carbon disks mounted on a sewing ring (Fig. 32.2) [3, 19]. Pyrolytic carbon is similar to graphite, but it is specifically designed and used for its resistance to thrombosis [3, 19].

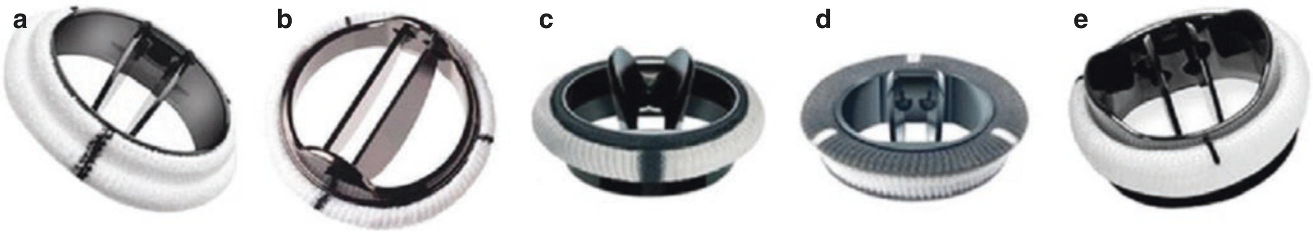

Fig. 32.2 Current aortic valve mechanical prostheses: Designs of current aortic valve prostheses: (**a**) Medtronic Open Pivot, (**b**) St. Jude Medical Regent, (**c**) LivaNova Bicarbon, (**d**) LivaNova CarboMedics, (**e**) CryoLife On-X. (Reproduced with permission from Kheradvar et al. Ann Biomed Eng. 2015 Apr;43(4):844–57 [3])

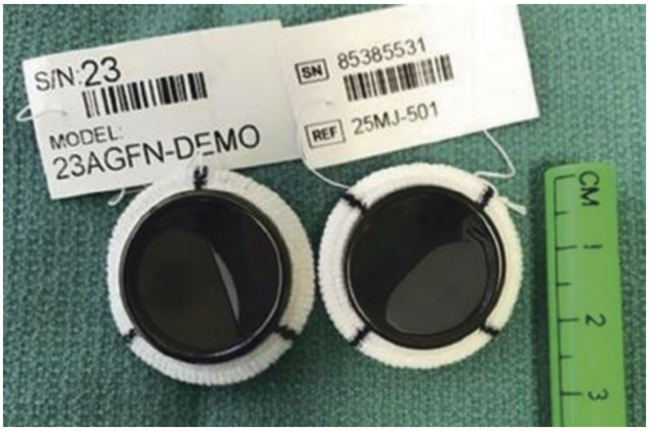

Fig. 32.3 St Jude valves: 23 mm Regent valve on left and 25 mm Masters HP on right demonstrating reduced sewing cuff size and a reduced frame diameter in the Regent to allow a greater orifice area for a given annular size. (Reproduced with permission from Barac et al. Ann Thorac Surg. 2018 Apr;105(4):1200–1204 [20])

St. Jude Medical (St. Paul, MN)

One of the first bileaflet mechanical valves on the market was the St. Jude Medical (St. Paul, MN) Masters Series, which was first implanted in 1977. The Masters Series is the most widely implanted prosthetic valve in the world and has remained unchanged except for redesigning the sewing ring. The first modification to the Masters series (Masters HP™ for high performance) included a reduction in the bulk of the sewing ring, which allowed for a one-size larger effective orifice implantation for a given annulus size. However, the most recent modification called the Regent valve has a modified external design that allows for larger orifice area without changing the pivot mechanism of the valve (Fig. 32.3) [20]. Further, the Regent is seated in the supra-annular position with only the pivot guards protruding into the annulus—making this an ideal valve for a small annulus [10, 21, 22]. While the Regent valve is only indicated for the aortic position, some have successfully used this device in the mitral position in patients with small annulus [20].

The St. Jude Medical mechanical valves have a long track record of excellent durability, hemodynamics, and freedom from adverse events [21–23]. In one study evaluating early hemodynamics, Bach et al. showed that the Regent valve had an average indexed effective orifice area >1.0 for all valve sizes at 6 months with an average mean gradient of 6.7 ± 3.9 [23]. St. Jude mechanical valves are also the only mechanical valves with up to 25 years in follow up documenting its durability. Emery et al. documented 32,190 patient-years of follow-up for patients with St. Jude mechanical valves and reported freedom from reoperation and valve thrombosis of 99% with only one mechanical failure in 6470 implants [21].

CryoLife (Kennesaw, GA)

The On-X mechanical valve was first implanted in 1996 and originally designed by On-X Life Technologies Holdings, Inc. (Austin, TX). In 2016 it was acquired by CryoLife (Kennesaw, GA) who has maintained the long track record of durability and safety. The On-X valve has several unique characteristics that make it particularly effective: (1) its valve leaflets and housing are made of pure pyrolytic carbon devoid of any silicone, which can be a nidus for platelet aggregation, (2) leaflets open 90°, have a shorter closing angle, and have actuated pivoting, which reduces turbulence and improves efficiency, and (3) the valve has two-point leaflet contact, leaflet guards, and inlet flare that prevent pannus ingrowth. Further, the design allows for rapid closure of the leaflets thereby intentionally producing large regurgitant washing jets that reduce potential for thrombosis while maintaining an overall small regurgitant volume [24–26]. The On-X valve also comes in a variety of sewing rings including the standard ring, a conform-x ring, and an anatomic ring. During implantation, the surgeon must ensure that the inlet flair fits through the annulus to prevent over sizing.

The unique design of On-X valves has shown excellent short and long term antithrombotic results. In the Prospective Randomized On-X Anticoagulation Clinical Trial (PROACT), the On-X valve was tested using a less rigorous anticoagulation strategy. A total of 375 patients were randomized to control (standard warfarin with International Normalized Ratio [INR] goal 2.0–3.0) or test (lower dose of

Warfarin 3 months after mechanical aortic valve replacement with INR goal 1.5–2.0). The study was able to demonstrate a significant reduction in major and minor bleeding events in the lower INR group with no difference in the incidence of stroke, transient ischemic attacks, or total all-cause mortality with an average of 3.8 years of follow-up [27]. This study has led to a revision in the AHA/ACC valvular heart disease guidelines to include that a lower target INR of 1.5–2.0 may be reasonable in patients with mechanical On-X aortic valve replacement (AVR) and no thrombotic risk factors [16].

The On-X valve has an excellent hemodynamic profile and long-term durability. The indexed orifice area in the early postoperative period was >1.0 for all valve sizes with comparable mean and peak gradients [28, 29]. In multiple follow-up studies including one with 12 years follow-up, there have been no structural failures reported and 0.1% mitral prosthesis thrombosis and 0% aortic prosthesis thrombosis [3, 25, 30, 31].

LivaNova (London, England)

First introduced in 1986, the CarboMedics mechanical valve (LivaNova, London, England) was originally produced by the Sorin Group until they merged with LivaNova in 2015. With both aortic and mitral iterations, the CarboMedics valve is composed of pyrolytic carbon with graphite substrate and has no pivot guards or struts, which improves the ease of implantation and theoretically improves blood flow. In addition to the CarboMedics line, LivaNova offers the Bicarbon line in Europe (not FDA approved in US), which includes several iterations that are designed for intra-annular (Fitline) or supra-annular (Overline, Simline) position. The advantage of the Overline is that it sits totally supra-annular without any intra-annular components, which allows the entire annulus size to be used for effective orifice area and is also ideal for double valve replacement. The size range for Overline is 16–24 mm [3]. LivaNova also makes an ascending aortic prosthesis called the Carbomedics Carbo-seal Valsalva (sizes 21–29 mm).

Outcomes of LivaNova valves are also well-documented. In one study with 17 years of follow-up in over 500 patients, there were no structural failures and only five patients required re-operation after AVR (4 for thrombosis, 1 for paravalvular leak), and 0 in the mitral valve replacement (MVR) group [32]. Further, in a post-hoc analysis of the LOWERING-IT trial testing lower INR goal (1.5–2.5) for mechanical AVR for LivaNova Bicarbon valves, the low INR group had no thromboembolic events and significantly lower bleeding events [33]. Similarly, in a study with 3300 patients with up to 20 years follow-up, the CarboMedics valve had no structural failures and a low rate of valve thrombosis (2.5% in those who underwent MVR and 0.3% in those who underwent AVR) [34].

Medtronic (Minneapolis, MN)

The Medtronic (Minneapolis, MN) line of mechanical valves consists of the Open Pivot line which was acquired from the valve company ATS (Minneapolis, MN) when Medtronic acquired ATS in 2010. First implanted in 1992, the Open Pivot design is composed of pyrolytic carbon coating with graphite substrate with a pivot design that features valve leaflets mounted on convex pivot guides that allows for no cavities in the valve ring. The Open Pivot line includes the intra-annular Open Pivot Standard and the supra-annular Open Pivot AP, which are available in the aortic and mitral position, as well as the Open Pivot AP360 that is designed solely for the supra-annular aortic position [3, 35].

The Open Pivot line has proven to be a durable and reliable mechanical valve with excellent hemodynamics. In a study including 1382 patients with up to 20 years follow-up that was 99% complete, there were no structural valve failures and acceptable incidences of valve thrombosis [36]. In another prospective randomized trial comparing CarboMedics, ATS (now Medtronic), and St Jude valves in the aortic position, there were no significant differences in gradients or left ventricular mass at 6 months [37].

Future Directions

The bulk of current and future research on mechanical valves is centered around trying to optimize flow dynamics, reduce platelet aggregation, and optimize hinge design in an effort to limit thromboembolism and the need for aggressive anticoagulation. There is mounting evidence that with the newer generation of mechanical valves, the need for anticoagulation with vitamin K antagonists with an INR goal of 2.5 or greater may not be necessary. In a recent metanalysis, data from the six randomized controlled trials evaluating the safety of lower INR goal for adults with mechanical AVR demonstrated significantly less bleeding with equivalent thromboembolic events [38]. Despite significant advances in mechanical valve design, all mechanical valves require lifelong anticoagulation, which remains the Achilles heel of mechanical valves.

Conclusions

The available bileaflet mechanical valves offer excellent hemodynamics with a low rate of thromboembolic events and remain the most durable option for valve replacement (Table 32.3). The choice of valve prosthesis—mechanical vs. bioprosthetic—must include discussions with the patient in which the risks of anticoagulation vs. the risks of valve

Table 32.3 Current mechanical aortic valves

Valve	Position	Sizes	Aortic effective orifice area (cm^2)[a]	Aortic mean gradient (mmHg)[a]	Advantages
St. Jude Regent	Aortic (Supra-annular)	19–27 mm	19 mm: 1.6 ± 0.4 21 mm: 2.0 ± 0.7 23 mm: 2.3 ± 0.9 25 mm: 2.5 ± 0.8 27 mm: 3.6 ± 0.5	19 mm: 11.0 ± 4.9 21 mm: 8.0 ± 4.8 23 mm: 6.9 ± 3.5 25 mm: 5.6 ± 3.2 27 mm: 3.5 ± 1.7	Low implant height, ideal for small annuli
CryoLife On-X	Aortic and Mitral (Intra-annular)	19–29 mm (aortic) 25–33 mm (mitral)	19 mm: 1.5 ± 0.2 21 mm: 1.7 ± 0.4 23 mm: 1.9 ± 0.6 25 mm: 2.4 ± 0.6	19 mm: 11.8 ± 3.4 21 mm: 9.9 ± 3.6 23 mm: 8.6 ± 3.4 25 mm: 6.9 ± 4.3	Lower INR goal after 3 months[b]
Medtronic Open Pivot AP	Aortic and Mitral (Supra-annular)	16–26 mm (aortic) 25–33 mm (mitral)	18 mm: 1.2 ± 0.3 20 mm: 1.3 ± 0.3 22 mm: 1.7 ± 0.4 24 mm: 2.0 ± 0.6 26 mm: 2.1 ± 0.4	18 mm: 21.0 ± 1.8 20 mm: 11.1 ± 3.5 22 mm: 10.5 ± 4.5 24 mm: 7.5 ± 3.1 26 mm: 6.0 ± 2.0	Continuous passive washing minimizes hemolysis, excellent hemodynamics, durability, and ease of implantation
LivaNova CarboMedics	Aortic and mitral (intra-annular)	19–31 mm (aortic) 23–33 mm (mitral)	19 mm: 1.0 ± 0.3 21 mm: 1.5 ± 0.4 23 mm: 1.4 ± 0.3 25 mm: 1.8 ± 0.4 27 mm: 2.2 ± 0.2 29 mm: 3.2 ± 1.6	19 mm: 18.9 ± 8.3 21 mm: 12.9 ± 5.4 23 mm: 11.0 ± 4.6 25 mm: 9.1 ± 3.5 27 mm: 7.9 ± 3.2 29 mm: 5.6 ± 3.0	Low profile ideal for low coronary ostia
LivaNova Bicarbon	Aortic (intra or supra-annular)	19–31 mm	19 mm: 1.4 ± 0.1 21 mm: 1.2 ± 0.4 23 mm: 1.5 ± 0.2 25 mm: 2.4 ± 0.3	19 mm: 16.7 ± 2.0 21 mm: 10.0 ± 3.3 23 mm: 7.7 ± 3.3 25 mm: 5.6 ± 1.6	Lower INR goal in low risk patients[c]

[a] Reproduced with permission from Zoghbi et al. J Am Soc Echocardiogr. 2009 Sep;22(9):975–1014 [29]

[b] In the United States an INR goal of 1.5–2.0 may be reasonable for patients with On-X AVR and no risk factors

[c] In Europe an INR goal between 1.5 and 2.5 is reasonable for patients at low risk for thromboembolism

degeneration are discussed. Available mechanical valves offer comparable hemodynamics, particularly in larger sizes; however, in smaller valve sizes, the On-X valve and St. Jude Regent valve may have superior hemodynamics. Ultimately, the choice of valve can be individualized based on surgeon preference and clinical scenario.

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33

Stented Bioprosthetic Values

Giuseppe Santarpino and Shahzad G. Raja

High Yield Facts

- The most frequently implanted biologic valve is a stented xenograft.
- The stented bioprosthetic valve may be an entire porcine valve, a composite from two or three individual pigs or made of bovine pericardium.
- Xenografts differ in the method of preservation of the valve cusps, the use of anticalcification regimens, and the composition and design of the stents and sewing rings.
- The LivaNova Crown PRT stented bioprosthesis is an innovative device built on the previous generation of the Mitroflow aortic valve model.
- The Trifecta valve is a third-generation heart valve that complements the St. Jude Medical Epic and Epic Supra bioprosthetic aortic valves.
- The Carpentier-Edwards PERIMOUNT Magna Ease is the most recent stented aortic bioprosthesis developed by Edwards Lifesciences, with a device design based on its two predecessor models (the PERIMOUNT and the PERIMOUNT Magna aortic valves).
- The Medtronic Mosaic Ultra valve is delivered with a Cinch® Implant System that facilitates aortic valve insertion, particularly through a tight sinotubular space and helps prevent suture "looping" around the stent posts for mitral valve replacement.
- Despite the advances in stent structure and anticalcification technology, contemporary stented bioprostheses suffer from the same disadvantages of the early models, including the risk of degenerative bioprosthetic stenosis or regurgitation and the need for suture lines.

Introduction

Over the past 50 years, a large variety of prosthetic valves have been developed with the aim of improving hemodynamic function, increasing durability, and reducing complications. Nevertheless, there is no ideal valve, and all prosthetic valves are prone to dysfunction. The valve types now implanted include bileaflet and tilting disc mechanical valves, stented porcine and pericardial xenografts, stentless porcine xenografts, cadaveric homografts, and autografts (Ross procedure). In patients with aortic root disease, composite grafts may be required to replace the aortic valve and root, usually necessitating coronary reimplantation. Recently, successful percutaneous aortic and pulmonary valve replacements have been accomplished. Prosthetic valves are broadly grouped as biologic or mechanical (Fig. 33.1). The most frequently implanted biologic valve is a stented xenograft [1]. These are composed of fabric-covered polymer or wire stents. The valve may be an entire porcine valve or a composite from two or three individual pigs. The cusps of stented pericardial xenografts are made from pericardium using a template and sewn inside or outside of the stent posts. Usually, the pericardium is bovine, but pericardium of other species has also been used. Xenografts also differ in the method of preservation of the valve cusps, the use of anticalcification regimens, and the composition and design of the stents and sewing rings as discussed below (Table 33.1).

Stented Aortic Bioprosthetic Valves

Crown PRT™ Valve

The LivaNova Crown PRT stented bioprosthesis (Fig. 33.2a) is an innovative device built on the previous generation of the Mitroflow aortic valve model. The valve design consists of a single bovine pericardium layer mounted outside the stent, combined with an advanced tissue treatment—the

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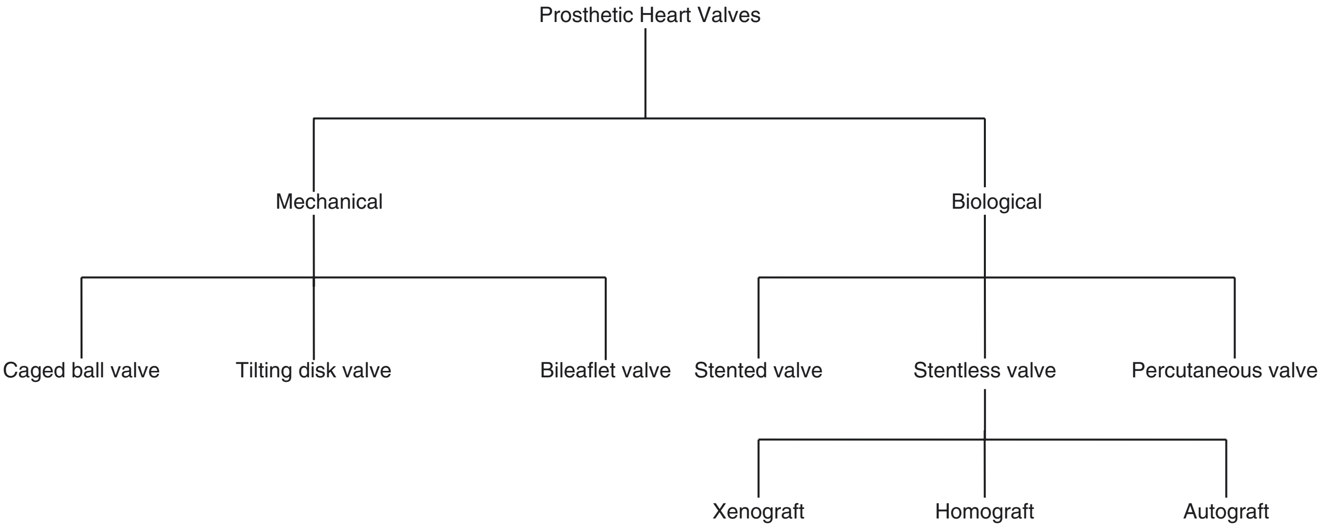

Fig. 33.1 Types of prosthetic heart valves

Table 33.1 Comparison of four commonly used latest stented aortic bioprosthetic valves

	Crown PRT	Trifecta	Magna ease	Mosaic ultra
Tissue	One single layer of bovine pericardium	One single layer of bovine pericardium	Three separate leaflets of bovine pericardium	Native porcine aortic valve
Stent	Resistant acetal homopolymer stent	Titanium alloy stent	Elgiloy (metallic alloy) stent	Acetal homopolymer Radiopaque eyelets of Haynes® alloy no. 25 at the commissures
Sewing ring	Streamlined shape	Silicone suture ring filler	Scalloped shape	The stent is covered with polyester fabric Scalloped shape
	Soft silicone filler, loaded with tungsten powder to achieve radiopacity	Polyester fabric	Soft, silicone-rubber filler	
	One-seam knit polyester fabric	Porcine pericardium cover	Porous, seamless polytetrafluoroethylene cloth	
	Commissure visible markers		Mid-commissure visible markers on Magna Ease only	
Construction	Tissue mounted on the outside of the stent	Tissue mounted on the outside of the stent	Tissue mounted inside the stent	The porcine aortic valve is excised, shaved at the muscle shelf and sutured to the cloth-covered stent
	Cross-stitch pattern to distribute stress on the commissures			
Tissue treatment				
Mitigation calcification treatment	Sorin Phospholipid Reduction Treatment (PRT) process	LinX AC Technology	Edwards ThermaFix process	The cross-linking with glutaraldehyde of the porcine aortic root tissue
Technology	Ethanol and 1,2 Octanediol	Ethanol	Ethanol and Tween80 and thermal treatment	Physiologic Fixation™
Mechanism of action	Remove phospholipids	Remove phospholipids Cap residual aldehydes Reduce cholesterol uptake Stabilize collagen	Remove phospholipids through Ethanol and Tween80 (XenoLogiX treatment) and unstable glutaraldehyde residual molecules through a thermal treatment	The cross-linking with glutaraldehyde of the porcine aortic root tissue
Storage solution	Formaldehyde	Formaldehyde	Glutaraldehyde	Glutaraldehyde
Rinsing procedure	Total rinse time: 2 min	Total rinse time: 20 s	Total rinse time: 2 min	Total rinse time: 60 s
	1-min rinse time in two rinse basins containing approximately 500 ml of sterile physiological saline solution	10-s rinse time in two rinse basins containing approximately 500 ml of sterile physiological saline solution	1-min rinse time in two rinse basins containing approximately 500 ml of sterile physiological saline solution	30-s rinse time in two rinse basins containing approximately 500 ml of sterile physiological saline solution

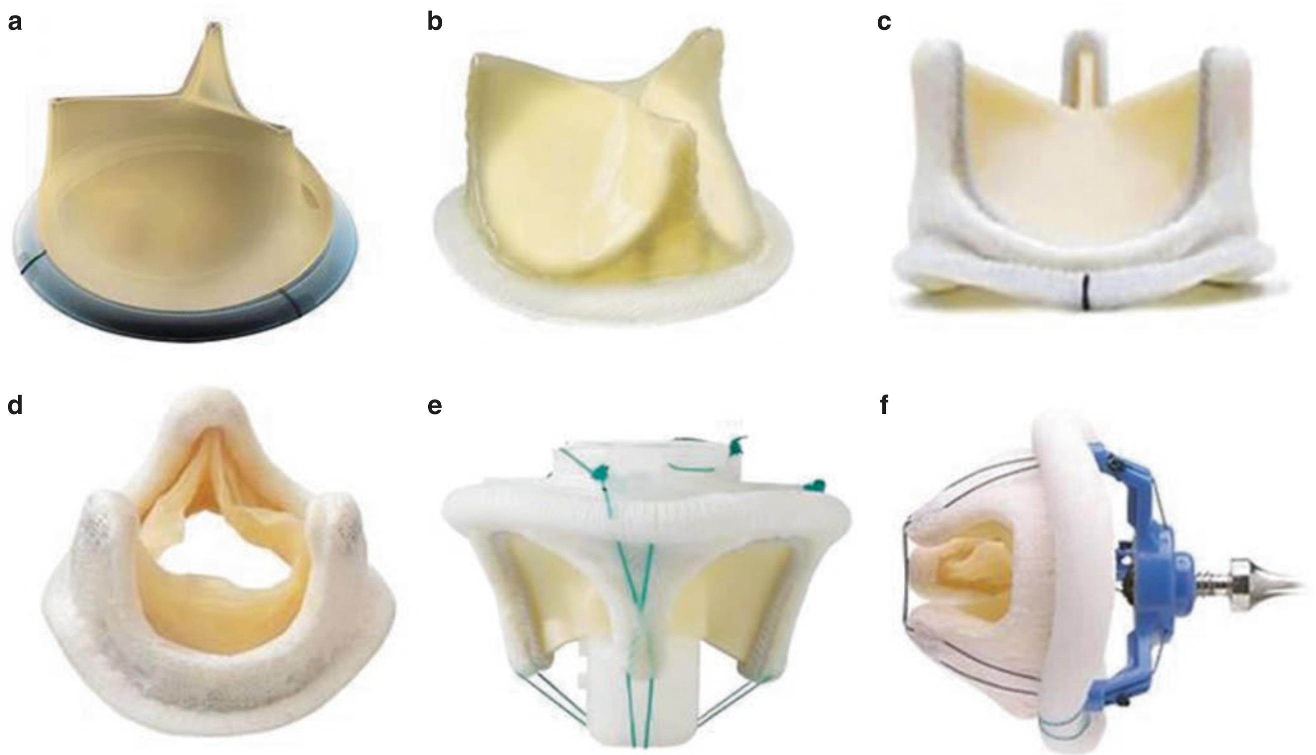

Fig. 33.2 Latest generation of stented bioprosthetic valves. (**a**) Crown PRT™ aortic valve. (**b**) Trifecta™ aortic valve. (**c**) Magna Ease™ aortic valve. (**d**) Mosaic Ultra™ aortic valve. (**e**) Perimount Plus Mitral™ valve. (**f**) Mosaic™ mitral valve

Phospholipid Reduction Treatment (PRT)—that is intended to bolster durability through mitigation of valve calcification. The Crown PRT bioprosthetic aortic valve can be implanted in either the supra-annular or intra-annular position. Since its market introduction in 1982, the Mitroflow pericardial bioprosthesis has demonstrated good long-term performance in multicenter studies [2, 3]. However, Sénage et al. [4] reported a high incidence of structural valve deterioration with the Mitroflow pericardial bioprosthesis. Although many aspects of this paper are questionable (e.g. too high incidence of patient-prosthesis mismatch in the published population) [5], the new Crown PRT pericardial bioprosthesis portends a better long-term durability. The Crown PRT bioprosthesis was developed as an evolution of the Sorin Mitroflow valve, where the pericardium layer is mounted outside the stent. The Mitroflow valve design was already shown to provide superior hemodynamic performance, especially in patients with small aortic annulus [6]. In addition, the Crown PRT ring is coated with Carbofilm that is thought to prevent thromboembolism. In a previous experience from our group with this device, thromboembolic events occurred in 1.1% of patients [7], a proportion significantly lower than that reported in a large series from the STS database [8]. However, our relatively limited sample size did not allow us to draw definite conclusions on this matter, and larger studies are warranted to confirm the benefits of Carbofilm in significantly reducing the risk of thromboembolic events.

Trifecta™ Valve

The Trifecta valve (Fig. 33.2b) is a third-generation heart valve that complements the St. Jude Medical Epic and Epic Supra bioprosthetic aortic valves. It is a tri-leaflet stented pericardial valve designed for supra-annular placement in the aortic position. The valve is fabricated using a polyester-covered titanium stent. The stent, excluding the sewing cuff, is then covered with porcine pericardial tissue. This covering is designed to provide protection from mechanical wear by allowing only tissue-to-tissue contact during valve function. A silicone insert in the polyester sewing cuff is slightly contoured to conform to the shape of the native annulus. The valve leaflets are fabricated from bovine pericardium. The porcine and bovine pericardium are preserved and cross-linked in glutaraldehyde. Glutaraldehyde, formaldehyde and ethanol are used in the valve sterilization process [9–14]. Additionally, the Trifecta valve is processed with Linx™ anticalcification technology, a patented proprietary anticalcification treatment that in animal studies has demonstrated resistance to calcification in four ways.

Magna Ease™ Valve

The Carpentier-Edwards PERIMOUNT Magna Ease (Fig. 33.2c) is the most recent stented aortic bioprosthesis developed by Edwards Lifesciences, with a device design based on its two predecessor models (the PERIMOUNT and the PERIMOUNT Magna aortic valves). The advanced Carpentier-Edwards PERIMOUNT Magna Ease aortic bioprosthesis adds enhanced implantability to the unsurpassed hemodynamics of the Magna valve platform—setting the new standard for tissue valve performance. In particular, the low valve profile enables easier insertion and aortotomy closure minimizing the risk for coronary obstruction. In addition, the presence of suture markers aids in valve orientation and suture placement. The implantation of the Carpentier-Edwards PERIMOUNT Magna Ease aortic valve seems to result in improved hemodynamic performance, as suggested by industry-leading effective orifice areas (EOA) and low gradients documented in multiple studies, with hemodynamic stability reported up to 17 years post-implantation [15–24]. According to the manufacturer, this model is designed for endurance as it is built on the proven performance of PERIMOUNT aortic valves, with over 27 years of clinical experience [23]. The Carpentier-Edwards ThermaFix process is the only anti-calcification technology designed to confront both major calcium binding sites. However, no clinical data are available to evaluate the long-term impact of the Edwards Lifesciences tissue treatment in patients.

Mosaic Ultra™ Valve

Medtronic offers three stented aortic bioprostheses, including the Hancock II, the Mosaic and the newest Mosaic Ultra tissue valve (Fig. 33.2d) that will be described here. The Mosaic Ultra valve is delivered with a Cinch® Implant System that facilitates aortic valve insertion, particularly through a tight sinotubular space and helps prevent suture "looping" around the stent posts for mitral valve replacement. It is mounted on a flexible stent that reduces tissue stress, making this bioprosthesis especially suited for minimally invasive procedures. Thirteen-year results demonstrate clinical safety and excellent performance [25]. Third-generation tissue technology—AOA® (alpha amino oleic acid) tissue treatment and Physiologic Fixation™—has improved the durability of this valve and helps mitigate valve calcification while preserving leaflet structure, with leaflets that function similarly to native aortic valves [26–28]. However, also in this case, no clinical data are available to evaluate the long-term impact of the AOA® tissue treatment and Physiologic Fixation process in patients. Because tissue valves open physiologically as native valves, they provide excellent forward flow. Different from the other bioprosthetic valves, the Mosaic Ultra is made from a single porcine aortic valve, using physiological pressure fixation that maintains the natural leaflet form and function. By contrast, aortic valve reconstruction with bovine pericardium is usually performed when using the other three valve models. The Mosaic Ultra has a reduced sewing cuff that allows greater flexibility to implant a larger valve size for improved hemodynamics.

Outcomes

Hemodynamic Performance

A number of studies evaluated the hemodynamic performance of stented aortic valves, though hemodynamic data mostly refer to predecessor models, as only scanty information is available in the literature on the latest generation of these valves.

It is difficult to compare data on the hemodynamic performance of stented pericardial and porcine aortic valves. It has been consistently demonstrated that aortic valve replacement with a pericardial bioprosthesis provides superior hemodynamic performance with better durability, resulting in significantly lower transvalvular gradients [29, 30]. Andreas et al. [31] compared a porcine prosthesis with a traditional pericardial heart valve with leaflets sutured inside of the stent and found that patients with a porcine bioprosthesis had a higher postoperative transvalvular gradient. Among stented pericardial tissue valves, the Crown PRT showed comparable mean gradients also in a subgroup analysis of the most common sizes with respect to other competing valves (i.e., St. Jude Medical Trifecta and Carpentier-Edwards PERIMOUNT Magna Ease) [31]. However, hemodynamic superiority and durability of pericardial versus porcine bioprostheses is still a matter of ongoing debate and, at present, there is no definite evidence of the advantage of one valve over the other.

Durability

Durability comparisons are made between the three types of pericardial aortic valves, given the different structural profile of the Mosaic Ultra porcine bioprosthesis. Also in this case, data are mostly derived from studies conducted with the predecessor models, which include longer follow-up periods. In particular, durability after aortic valve replacement with the Mitroflow and PERIMOUNT pericardial bioprostheses is evaluated, as no long-term follow-up data are available for both the Crown PRT and Magna/Magna Ease valves. Conversely, mid-term data are available for the Trifecta valve.

Stented Mitral Bioprosthetic Valves

PERIMOUNT Plus Mitral™ Valve

The Carpentier-Edwards PERIMOUNT Plus Mitral heart valve is the first—and only—biomechanically engineered valve (Fig. 33.2e). It combines the latest engineering advancements with the benefits of natural pericardial tissue. It is built on the proven long-term durability of the PERIMOUNT valve in the mitral position and exposed to XenoLogiX tissue treatment that eliminates up to 98% of phospholipids, a major calcium binding site. Integrated processes such as stress-free Neutralogic fixation, PeriMap pericardial thickness mapping technology, and tissue deflection testing enable leaflets to be accurately matched.

Mosaic Mitral™ Valve

The Mosaic Mitral valve (Medtronic, Inc., Minneapolis, MN) (Fig. 33.2f) is obtained from the porcine aortic valve, then mounted on a low-profile, flexible, acetyl copolymer stent that is covered with polyester fabric. The valvular tissue is treated with α-amino oleic acid, which has been shown to mitigate cusp calcification in animal studies [27], and then undergoes physiologic fixation at zero pressure, which helps to maintain the leaflet structure and root geometry of fresh aortic valves. The Mosaic Mitral valve is provided with the Cinch® II implant system (Medtronic, Inc., Minneapolis, MN), which enables inward bending of the posts and thereby helps to prevent looping of the sutures around the struts during mitral valve replacement; on the sewing ring, a green suture marker aids in orientation of the prosthesis when used in the mitral position.

Outcomes

Hemodynamic Performance

Currently no data is available for the PERIMOUNT Plus Mitral heart valve. However, long-term data for its predecessors is encouraging and establishes the superiority of stented pericardial bioprosthesis in the mitral position amongst biological valves available for mitral valve replacement. Firstenberg and colleagues [32] were the first to report on hemodynamic performance of the PERIMOUNT mitral prosthesis. Sixty-nine patients, at seven international centers, between January 1996 and February 1997 consented to participate in a short-term echocardiography follow-up. Echocardiographs were collected at a mean of 600 ± 133 days after implantation (range, 110–889 days); all underwent blinded core lab analysis. At follow-up, peak gradients were 9.09 ± 3.43 mmHg (mean, 4.36 ± 1.79 mmHg) and varied inversely with valve size ($p < 0.05$). The effective orifice areas were 2.5 ± 0.6 cm^2 and tended to increase with valve size ($p = 0.08$). Trace mitral regurgitation (MR) was common ($n = 48$), nine patients had mild MR, one had moderate MR, none had severe MR. All MR was central ($n = 55$) or indeterminate ($n = 3$). No paravalvular leaks were observed. Mitral regurgitation flow areas were 3.4 ± 2.8 cm^2 and were without significant volumes. Goetze et al. [33] also reported short-term Doppler echocardiographic data (7.6 ± 13 days postoperatively) of 189 patients (110 women; 68 ± 12 years of age) who had PERIMOUNT mitral prosthesis implanted between September 2000 and May 2002. For all valves, the peak velocity was 1.9 ± 0.3 m/s, peak gradient was 15 ± 4.8 mmHg, and mean gradient was 5.8 ± 2 mmHg. The pressure half-time was 93 ± 24 ms, with a calculated effective orifice area of 2.5 ± 0.6 cm^2. The average effective orifice area by continuity equation (83 valves) was 1.5 ± 0.5 cm^2. The mitral regurgitation was graded mild or less in 97.5% of all valves.

Celiento et al. [34] reported good hemodynamic performance of Medtronic Mosaic valve in the mitral position at 17 years follow-up. At echocardiography, 24 patients with 27-mm prostheses showed a mean gradient of 5 ± 1.7 mmHg and an effective orifice area of 1.57 ± 0.3 cm^2; in 16 patients with 29-mm prostheses, the mean gradient was 4.5 ± 1.9 mmHg, and the effective orifice area, 1.63 ± 0.4 cm^2. Jamieson and colleagues [35] reported similar hemodynamic performance data for 232 Mosaic mitral prostheses (sizes 25–31 mm) at a mean follow-up of 7.3 years. The mean diastolic gradient range was 6.7 ± 1.7 to 3.7 ± 0.9 mmHg and effective orifice area range was 1.9 ± 0.3 to 2.4 ± 0.6 cm^2.

Durability

Bourguignon et al. [36] reported excellent very late outcomes for the Carpentier-Edwards pericardial bioprosthesis in the mitral position. At 20 years, the overall actuarial survival rate was 16.9% ± 3.9% for their cohort of 404 patients who had 450 pericardial bioprostheses in the mitral position. The mean age of the cohort was 68 years. The actuarial freedom from complications at 20 years was thromboembolism, 83.9% ± 7.6%; hemorrhage, 80.2% ± 10.8%; endocarditis, 94.8% ± 1.4%; structural valve deterioration, 23.7% ± 6.9%; and explantation owing to structural valve deterioration, 40.5% ± 8.0%. The competing risk analysis demonstrated an actual risk of explantation owing to structural valve deterioration at 20 years of 25.5% ± 2.9%. The expected valve durability was 16.6 years for the entire cohort (11.4, 16.6, and 19.4 years for patients aged <60, 60 to 70, and >70 years, respectively).

Similar good clinical outcomes and durability data has been reported for Medtronic Mosaic valve by Celiento and colleagues [34]. They reviewed the clinical data of 100 patients at a mean follow-up of 6 ± 4.6 years (maximum = 17.7 years). The early mortality rate was 10% (6% in elective patients); late deaths occurred in 31 patients (5 valve-related). Actuarial survival rates at 5, 10, and 15 years were 74% ± 5%, 50% ± 6%, and 37% ± 8%. The mean NYHA class in survivors was 1.4 ± 0.6 ($p < 0.0001$). Thromboembolic episodes occurred in four patients, with an actuarial freedom at 15 years of 91% ± 5%. No cases of endocarditis were observed. Four patients needed reoperation, two for structural failure, and one each for perivalvular leakage and valve thrombosis. Actuarial freedom from structural failure and from reoperation, respectively, was 93% ± 5% and 91% ± 5% at 15 years.

Currently no studies are available comparing stented pericardial and porcine mitral valve prostheses.

Conclusions

Most of the above-described types of stented bioprosthetic valves have only recently been introduced into the market, which makes direct comparisons challenging. Second and third-generation prosthetic valves have been considered and, hence, comparative analysis is of limited value. The data derived from the different studies also pose interpretation issues, either because of the small sample size or because each cardiac surgery center usually performs valve replacement predominantly with the same prosthesis model, which further limits interstudy comparisons. Despite the advances in stent structure and anticalcification technology, contemporary stented bioprostheses suffer from the same disadvantages of the early models, including the risk of degenerative bioprosthetic stenosis or regurgitation and the need for suture lines. Future research should aim at developing faster and easier suturing techniques, so as to compete with sutureless devices and achieve shorter implantation and ischemic times—the Cinch® Implant System on the Mosaic Ultra valve partially meets this need. In addition, further refinement in the field of biomaterials should be pursued to obtain more ideal prostheses and minimize the risk for immunoreaction and bioprosthetic valve failure. The expansion of the prosthetic heart valve market to emerging countries and failure to eradicate several infectious and inflammatory diseases (e.g., rheumatic heart disease in developing areas of the world) are expected to draw interest in the development of more ideal prosthetic devices. This means that hopefully in the near future, stented bioprostheses will be biocompatible, less expensive, free from the risk of valve degeneration, will not require anticoagulation, and will adapt to patient growth from childhood into adulthood.

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Bentall and Mini-Bentall Procedure

34

Adam Chakos and Tristan D. Yan

High Yield Facts

- The Bentall procedure and its modifications are the gold standard for treating aortic root pathology.
- The modified Bentall procedure has evolved over 50 years and involves replacement of the entire aortic root and valve with a composite valve graft and reimplantation of the coronary buttons.
- The early- and long-term results of modified Bentall procedure are excellent.
- The mini-Bentall procedure is performed through an upper mini-sternotomy.
- Published data for outcomes of the mini-Bentall procedure are presently limited.
- Current available evidence suggests that mini-sternotomy is a safe, feasible alternative option to full sternotomy in aortic root replacement.

Introduction

The Bentall procedure was originally described in 1968 by Bentall and De Bono for treatment of a dilated aortic root with aortic incompetence [1] and involves replacement of the aortic valve, root and ascending aorta. Since that seminal paper, the Bentall procedure has undergone many evolutions (Table 34.1), such as the "Cabrol Procedure" (where a separate graft is used to perfuse the coronaries) [2] and the now commonly utilized "Button Bentall" (where the coronary buttons are excised from the native aorta, mobilized and re-implanted appropriately on the graft) [3]. The original work by Bentall and De Bono also formed the basis of the well-known valve-sparing root replacement procedures of David [4] and Yacoub [5], avoiding long-term anticoagulation or late redo in bioprosthesis recipients (Fig. 34.1).

Indications for the procedure and its variants include proximal aortic dilatation with involvement or congenital abnormality of the aortic valve, proximal aortic dissection (acute and chronic), aortic rupture, intramural hematoma, and destruction of the aortic valve and root by endocarditis or calcification [6]. Surgical management with the Bentall procedure offers good patient outcomes, with a recent meta-analysis of 7629 patients from 46 studies demonstrating an annual mortality rate of 2% with 6 years follow-up [7]. Recent retrospective series have demonstrated 5-year Kaplan-Meier survival between 80% and 90% [8–12].

This chapter has already touched upon the Bentall procedure and will focus on the step-by-step performance of the minimally invasive ("mini") Bentall procedure, including the "French Cuff" technique for bioprosthetic valves [13, 14]. The minimally invasive approach offers less requirement for blood transfusion, reduced post-operative pain, reduced respiratory complications, earlier extubation and shorter hospital length of stay [15, 16]. The mini-Bentall procedure and minimally invasive approach to the proximal thoracic aorta are technically feasible, with the efficacy and superiority of the technique currently being prospectively evaluated [17].

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Table 34.1 Evolution of the Bentall procedure

Year	Procedure	Note
1956	Cooley & De Bakey reported the first successful replacement of a fusiform ascending aneurysm	Cardiopulmonary bypass used
1964	Myron Wheat reported his team's efforts to replace the entire ascending aorta	Their approach to the displaced coronary ostia was to resect the aorta 1.5–2 cm proximal to this level, while leaving a tongue of tissue surrounding the two coronary take-offs
1968	Bentall & De Bono published their classic report describing a technique for complete replacement of the ascending aorta	The classic Bentall procedure used a composite valve-graft prosthesis with a mechanical valve and had the side-to-side anastomosis of the coronaries to the aortic prosthesis
1976	Blanco and colleagues used an interposition conduit as an extension from the neoaorta to coronary artery	Initially Dacron® and then later a saphenous vein graft was used. Direct end-to-end anastomosis from the coronary ostia was performed
1976	Zubiate & Kay sutured closed the coronary ostia, and then performed an end-to-side anastomosis onto the corresponding coronary artery	Saphenous vein graft was used
1978	Cabrol described his modification of the Bentall procedure	A single, 8 mm Dacron® tube was used that functioned to supply the entire coronary circulation. The aneurysmal wall was closed over the revision, and a 1.5 cm fistula was created to the right atrial appendage
1982	Piehler & Pluth described the hybrid approach for dealing with the coronary arteries	The left coronary required a conduit due to insufficient displacement for direct anastomosis. The mobility of the right coronary permitted direct connection to the aortic graft via an inclusion technique. A beveled Gore-Tex® interposition graft was used
1991	Kouchoukos described the technique of using "coronary buttons"	Kouchoukos began preclotting the Dacron® graft with albumin to reduce permeability
1993	Sarsam & Yacoub reported the remodeling technique for valve-sparing root replacement	Lack of stabilization of the aortic annulus was a major drawback of the technique
1996	Tirone David reports experience with the reimplantation technique of valve-sparing root replacement	This approach had the benefit of stabilizing the aortic annulus by sewing the native valve directly into a Dacron® graft of a fixed circumference. To date 5 iterations (I to V) of the procedure have been reported

Mini-Bentall Procedure

The mini-Bentall procedure follows the principles of traditional aortic root replacement surgery. Despite the smaller incision, meticulous surgical technique and methodical execution provides unhindered visualization at each stage of the procedure. The next sections will cover the planning and execution of the mini-sternotomy and the surgical steps of the mini-Bentall procedure: institution of cardiopulmonary bypass, aortotomy, root and valve preparation, valve-graft interposition, coronary button re-implantation, distal anastomosis and closure. Mini-access hemi-arch replacement is also outlined for cases involving distal ascending aortic pathology.

Mini-sternotomy

The skin incision and caudal extent of the mini-sternotomy is planned by examining contrast-enhanced computed tomographic images. The position of the aortic annulus and the corresponding intercostal space above should be identified. This is typically the fourth or fifth intercostal space. Next, the patient is exposed and the location of the supra-sternal notch, manubrio-sternal junction, xiphisternum and intercostal spaces above and below the aortic annulus demarcated with a marking pen. The femoral arteries are identified and marked and the patient washed with antiseptic solution and draped to leave the precordium and groin areas exposed.

An approximately 5 cm midline skin incision is made from the manubrio-sternal junction to the third intercostal space (Fig. 34.2). Diathermy is used to extend the incision down onto the body of the sternum, to the supra-sternal notch superiorly and to the sternal edges laterally. The bridging vein atop the manubrium is clipped and resected. A subcutaneous drain is inserted parasternally one intercostal space below the inferior limit of the skin incision and passed along the length of the midline incision. Intra-operatively, the subcutaneous drain will be utilized for carbon dioxide insufflation (to prevent air embolism) and after surgery, it will be left in place to allow subcutaneous drainage and reduce the formation of seroma.

A pneumatic or electric bone saw is used to develop a mini-sternotomy starting from the supra-sternal notch and moving inferiorly to terminate at the left parasternal space (a right mini-sternotomy is rarely used). Bone wax is appropriately applied and the thymic fat pad mobilized superiorly to the level of the innominate vein and resected (to improve exposure).

The pericardium is incised as an inverted "T" from the pericardial reflection (superiorly) to the fourth intercostal space. Three pericardial traction sutures are placed on each side and secured to the skin incision. A minimally-invasive

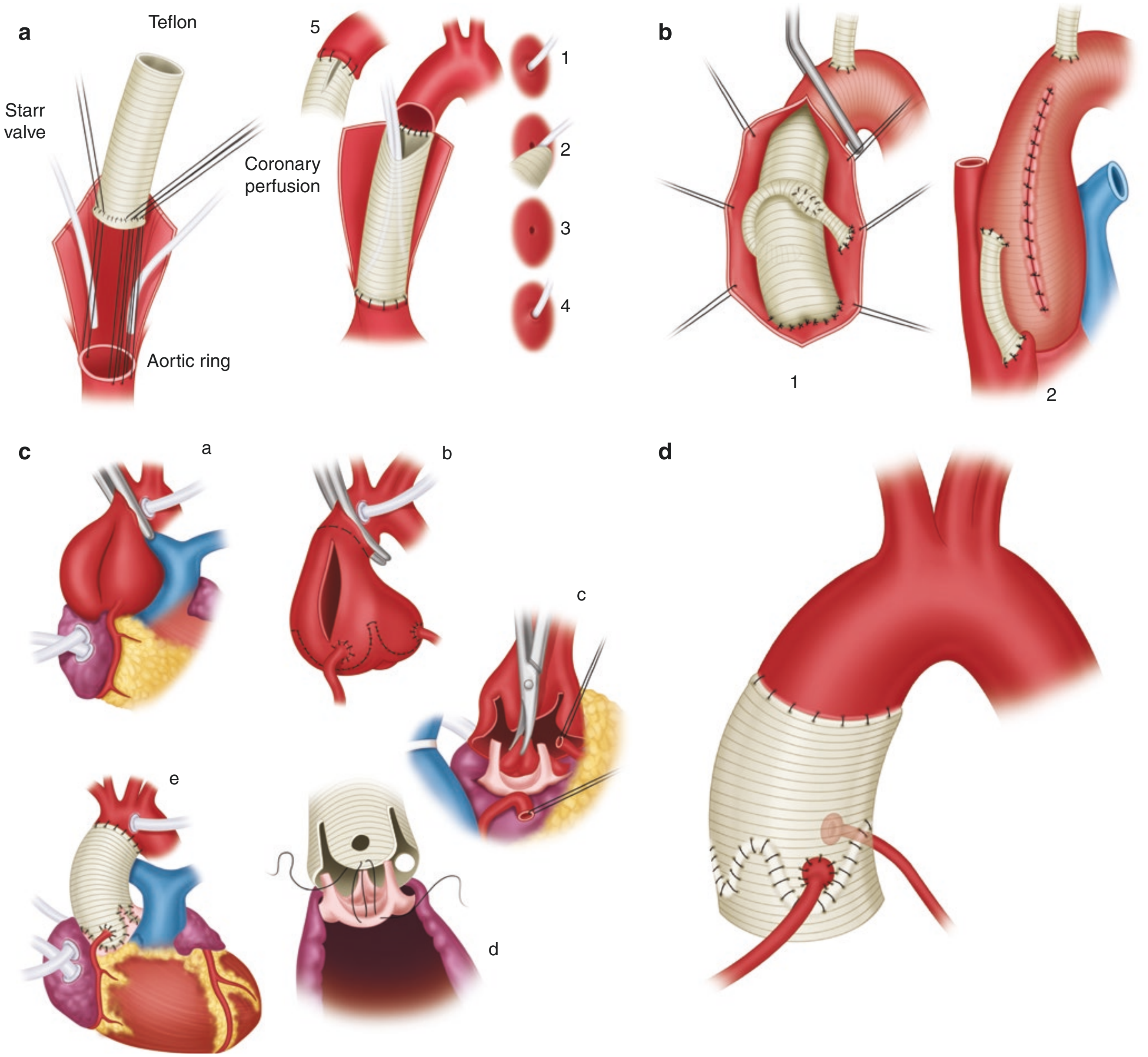

Fig. 34.1 The classical Bentall procedure and its modifications. (**a**) Classical Bentall procedure. (**b**) Cabrol procedure. (**c**) Yacoub's remodeling valve-sparing root replacement. (**d**) David's reimplantation valve-sparing root replacement. (Figure reproduced with the permission of Beth Croce and *Bioperspective*)

sternal retractor is then inserted between the hitched pericardium and opened to expose the ascending aorta. Further exposure and limited mobilization of the aorta is obtained by dissecting out the plane between the aorta and pulmonary artery (Fig. 34.3).

Cardiopulmonary Bypass

After systemic heparinization to an activated clotting time (ACT) of at least 450 s, peripheral venous cannulation is performed. A guidewire is inserted from the femoral vein to the superior vena cava under trans-oesophageal echocardiographic (TOE) guidance. Serial gradual dilations and insertion of a 25 Fr multi-stage venous cannula is performed, with TOE used to confirm the cannula tip is located in the superior vena cava to optimize venous return.

The venous cannula is connected to the cardiopulmonary bypass (CPB) machine and arterial cannulation is performed femorally or through the distal ascending aorta. In most cases, central aortic cannulation is the preferred approach to reduce the risk of retrograde embolism.

For aortic root replacement, core body temperature is cooled to 32 °C. In cases where hemi-arch replacement is

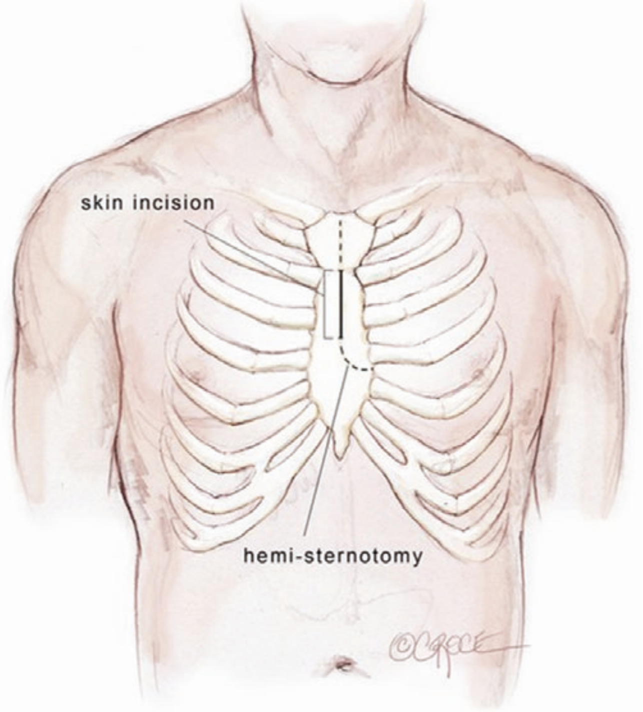

Fig. 34.2 Surface landmarks for the Mini-Access Bentall procedure. (Figure reproduced with the permission of Beth Croce and *Bioperspective*)

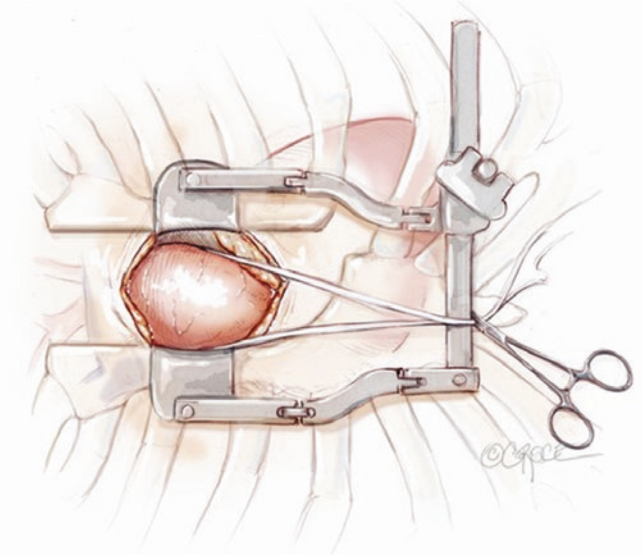

Fig. 34.3 Insertion of mini-sternotomy retractor and exposure. (Figure reproduced with the permission of Beth Croce and *Bioperspective*)

necessary, cooling to 25 °C is advised. Hemi-arch replacement also requires configuration of the arterial inflow line to provide selective cerebral perfusion while the distal open anastomosis is performed.

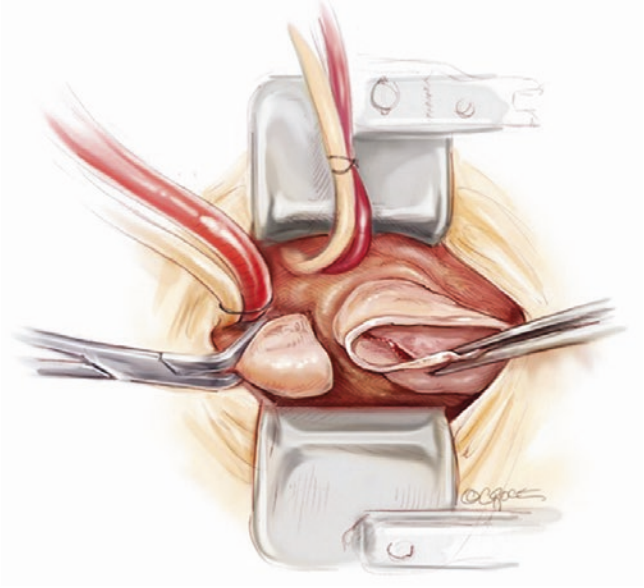

Fig. 34.4 Resection of aneurysmal aorta, leaving 1 cm of tissue proximal to the cross-clamp and 1 cm above the aortic annulus. (Figure reproduced with the permission of Beth Croce and *Bioperspective*)

Aortic Root Exposure

While cooling the bypass, flow is reduced and the distal ascending aorta is cross-clamped. Cold blood or Custodial cardioplegia can then be delivered in an antegrade fashion through the aortic root cannula or via direct coronary ostial cannulation where aortic incompetence exists. Retrograde cardioplegia is not necessary.

Aortotomy is performed and the diseased ascending aorta is resected, sparing a 1 cm cuff of aorta proximal to the cross-clamp. The aortic root and valve are inspected and the aneurysmal aorta is resected, leaving 1 cm of aortic tissue above the annulus (Fig. 34.4). The coronaries are then separated from the aortic root as buttons, ideally allowing at least 3 mm of tissue circumferentially around the coronary ostia. The buttons should be left to rest in their anatomical position.

A pledgeted 2-0 Ethibond traction suture (Ethicon, Somerville, NJ) is placed just above each commissure. The commissural traction sutures are then hitched to the edges of the adjacent skin so that the root is brought anteriorly and superiorly to expose the aortic leaflets. In the case of a non-tricuspid aortic valve, the traction sutures should be placed 120° apart to ensure the annulus is adequately presented for valve resection (Fig. 34.5).

Resection of the aortic leaflets is performed. Calcified annulus should be debrided. To avoid any particles falling into the left ventricle, a ribbon gauze may be inserted into the ventricle to catch any fragments during decalcification.

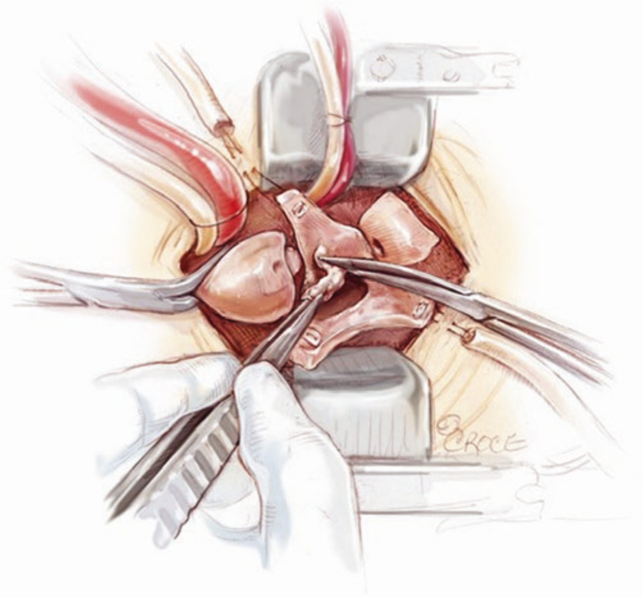

Fig. 34.5 Resection of calcified annulus. Note the three commissural traction sutures providing excellent exposure of the aortic root. (Figure reproduced with the permission of Beth Croce and *Bioperspective*)

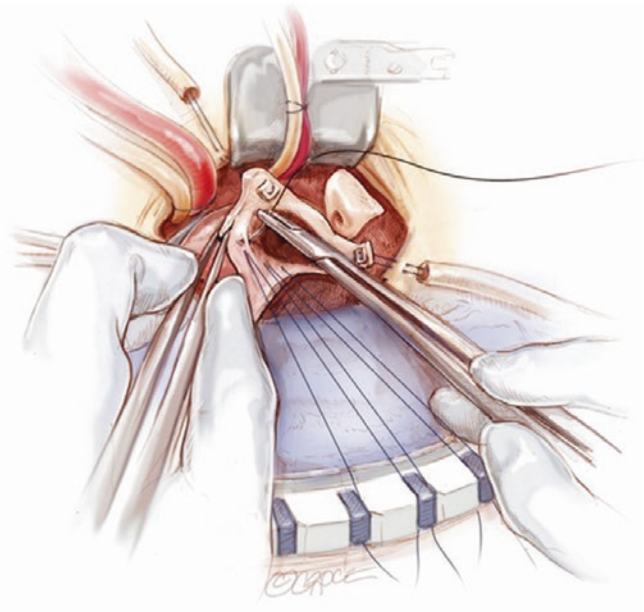

Fig. 34.6 Placement of pledgeted 2-0 Ethibond sutures on the inferior surface of the aortic annulus. (Figure reproduced with the permission of Beth Croce and *Bioperspective*)

The "French Cuff" Technique

In cases where a bio-root is required (using a tissue valve and Dacron graft), the "French Cuff" technique is favored to improve hemostasis. With the annulus prepared, pledgeted 2-0 Ethibond Excel annular horizontal mattress sutures are placed on the inferior surface of the aortic annulus (Fig. 34.6). The sutures should be evenly spaced, with pledgets abutted to ensure equal distribution of annular tension and a tight seal around the prosthesis (when later seated). Sizers are then used to identify the correct diameter valve prosthesis.

To apply the "French Cuff" technique, the tube graft selected should be 5 mm greater in diameter than the valve size:

$$\text{Graft size} = \text{Aortic valve size} + 5\,\text{mm}$$

The proximal cuff of the Valsalva graft is trimmed to 8 mm. The skirted portion is folded back over the outside of the Valsalva graft to form a double cuff (hence, the name "French Cuff"). The valve is then positioned inside the graft and the annular suture needles are passed through the valve sewing ring and everted edge of the Valsalva graft one by one.

Once all annular sutures have been passed through the sewing ring, the valve and graft are parachuted down to the annulus and the sutures are tied down (Fig. 34.7). The prosthesis is secured using a tension sequence, tying three sutures 120° apart first (for example, at the nadirs of a bioprosthesis), then tying those between them. This ensures even seating and sealing of the valve ring onto the annulus.

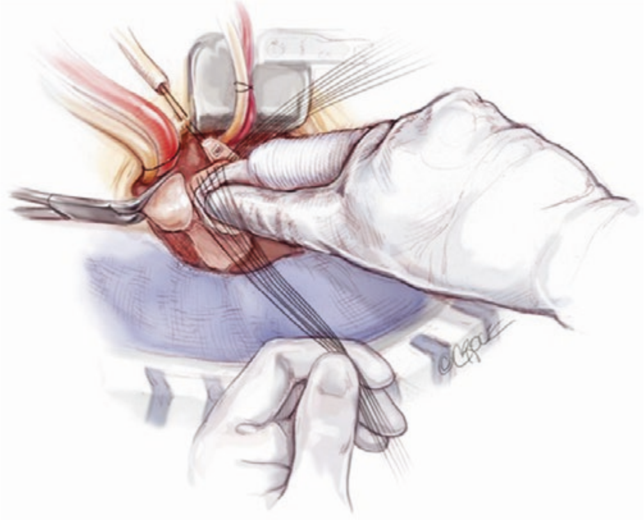

Fig. 34.7 Parachuting of the valve and graft is performed by holding the annular sutures in one hand along the axis of the left ventricular outflow tract and pushing the valve and graft down onto the annulus with the other hand. (Figure reproduced with the permission of Beth Croce and *Bioperspective*)

The "French Cuff" technique allows hemostasis to be achieved using a second layer of sutures incorporating the everted edge of the cuff and the remnant of the aortic wall [18].

Coronary Button Re-implantation

The exact implantation location of the coronary buttons on the tube graft is determined by momentarily filling the heart to relieve any rotation that would otherwise put tension on the coronary anastomoses if they were made in the unloaded state. After marking the coronary button positions on the graft, the heart is offloaded. Ophthalmic cautery is used to create holes on the graft. The buttons are then sewn onto the graft using full-thickness bites of a continuous 5-0 polypropylene suture (Fig. 34.8).

With the buttons secured, the valve conduit is ready for pressure testing. Delivery of a full dose of antegrade cardioplegia will ensure the valve is competent and the aortic annulus and coronary anastomoses are hemostatic. Systemic re-warming can then be commenced.

Distal Anastomosis

With the heart filled, the graft is stretched and the point that it meets the distal aorta marked for trimming and angular position. The graft is appropriately opposed to the distal aorta and a continuous 3-0 polypropylene suture used, starting on the posterior wall at the 4 o'clock position (away from the surgeon—Fig. 34.9). The suture is continued clockwise around to the 11 o'clock position, using a nerve hook to maintain adequate tension on the suture line. To improve hemostasis, pledgeted 4-0 running prolene reinforcing sutures can additionally be used on the back wall. It is important to apply this layer of hemostatic pledgeted sutures at this stage on the inside of the graft.

The anastomosis is completed by continuing the running suture from the 4 o'clock position counter-clockwise to the 11 o'clock position. An aortic root vent is inserted prior to tying the suture ends. With the vent in place, the table is moved to the Trendelenburg position, the lungs inflated and heart filled. The graft is de-aired using the vent and the aortic cross-clamp released.

Hemi-Arch Replacement

When distal ascending aorta pathology exists, hemi-arch replacement is required. In this case, the patient will require systemic cooling to 25 °C and selective cerebral perfusion for the open distal anastomosis.

The hemi-arch replacement is commenced with the cessation of aortic perfusion, removal of the aortic cross clamp and subsequent resection of the diseased distal segment, including the original aortic cannulation site. Direct visualization of the arch vessels allows for assessment of luminal disease and cannulation for cerebral perfusion, using a unilateral or bilateral strategy as appropriate (Fig. 34.10).

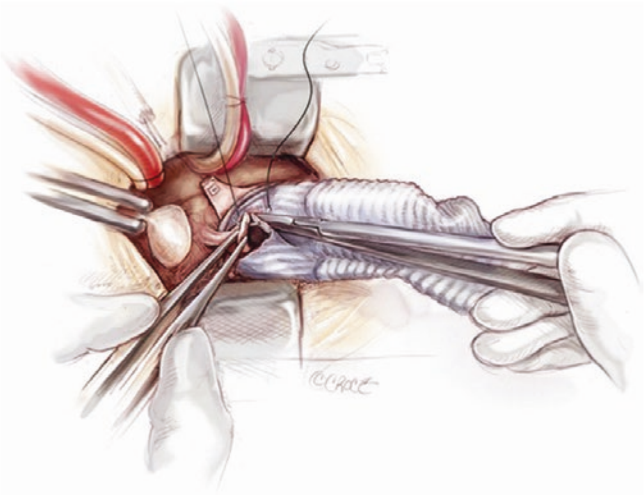

Fig. 34.8 Re-implantation of the left coronary button onto the tube graft using a continuous 5-0 polypropylene suture. (Figure reproduced with the permission of Beth Croce and *Bioperspective*)

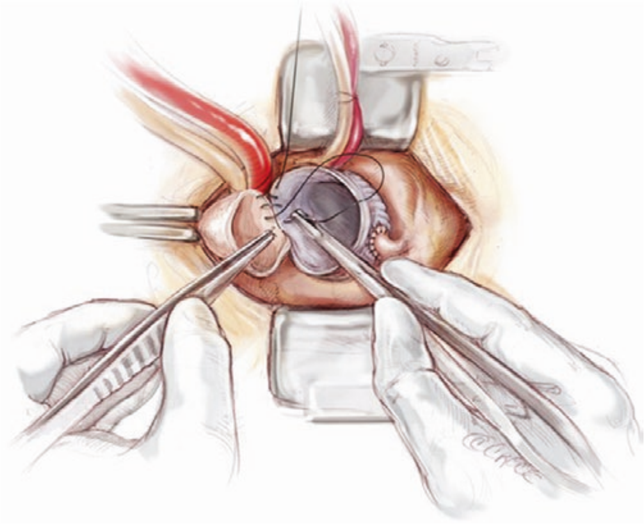

Fig. 34.9 Placement of continuous 3-0 polypropylene suture to anastomose the tube graft and distal aorta, starting on the posterior wall. (Figure reproduced with the permission of Beth Croce and *Bioperspective*)

A graft with a perfusion side-arm is selected and the open distal anastomosis performed starting posteriorly (away from the surgeon) with a continuous 3-0 polypropylene suture (Fig. 34.11). The anterior portion of the distal anastomosis is completed and if further reinforcement of the anastomosis is required, additional pledgeted 4-0 sutures can be placed. The cerebral perfusion cannula is then removed from the distal anastomosis line, the side-arm of the graft connected to the arterial line of the CPB machine and the graft clamped proximally. The patient is then re-perfused via the sidearm of the graft and re-warming is commenced.

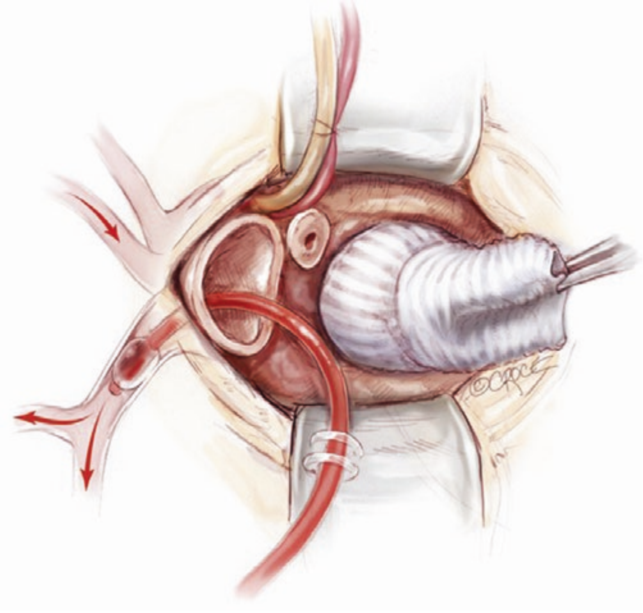

Fig. 34.10 Cannulation of the innominate artery for unilateral cerebral perfusion. The diseased distal aortic segment has been resected and the epi-aortic vessel lumen inspected for disease. (Figure reproduced with the permission of Beth Croce and *Bioperspective*)

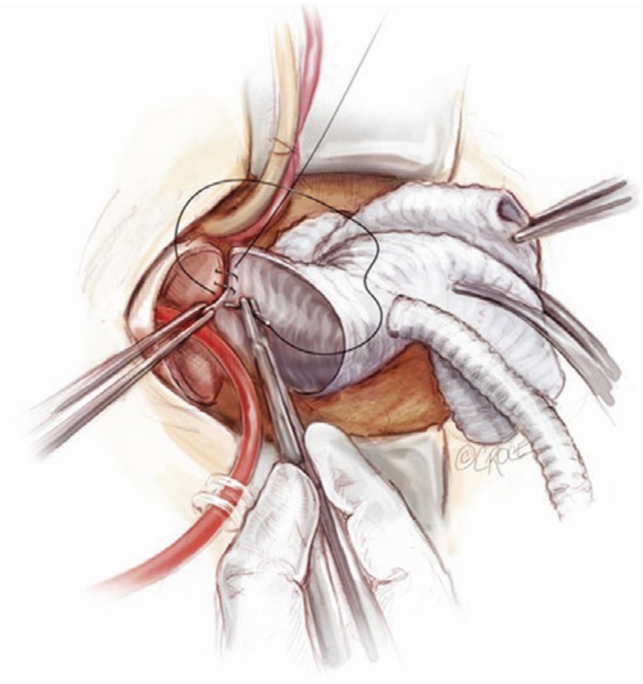

Fig. 34.11 Open distal anastomosis of side-arm graft and distal aorta using continuous 3-0 polypropylene suture. Cerebral perfusion cannula is in place. (Figure reproduced with the permission of Beth Croce and *Bioperspective*)

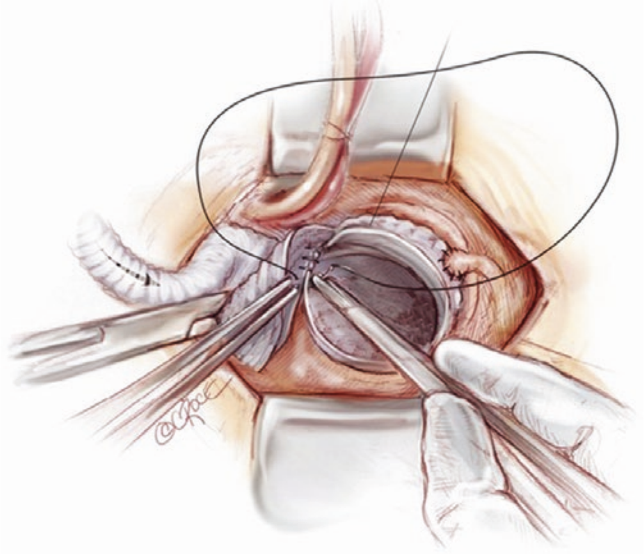

Fig. 34.12 Graft-graft anastomosis with continuous 3-0 polypropylene suture. Additional 4-0 pledgeted sutures can be used if required. Note the cross clamp in place on the proximal hemi-arch graft and perfusion using the graft side-arm. (Figure reproduced with the permission of Beth Croce and *Bioperspective*)

Connection of the root and hemi-arch grafts is completed by stretching them to ascertain the graft-graft anastomosis point and trimming the hemi-arch graft to size. The grafts are anastomosed with continuous 3-0 polypropylene sutures, with sutures placed no more than a couple of millimeters apart (Fig. 34.12). The cross-clamp can then be released and the grafts de-aired by placement of a 21-gauge needle. If required, additional pledgeted 4-0 prolene sutures are placed for improved hemostasis.

Closure

Epicardial pacing wires are inserted on the surface of the right ventricle and a 28 Fr soft drain is placed and brought out below the xiphoid cartilage. The patient is weaned from CPB and protamine given. The surgical site is packed with small sponges for a 10-min hemostatic pause. When hemostasis is verified, the sponges are removed and the sternum approximated using stainless steel wires. Fascial and subcuticular closure concludes the procedure.

Outcomes

Currently there is limited data comparing mini-Bentall with conventional full sternotomy Bentall. A recently published meta-analysis of 2765 patients from eight comparative studies [19] reported that mini-sternotomy aortic root replacement was associated with significantly shorter CPB time ($p = 0.009$), lower rate of blood transfusion ($p = 0.01$), lower operative mortality ($p = 0.02$), and shorter intensive care and hospital ($p = 0.0009$, $p = 0.03$) lengths of stay, respectively.

However, there was no difference between mini-sternotomy and conventional aortic root replacement in terms of aortic cross-clamp time ($p = 0.28$), total operation time ($p = 0.31$), re-exploration rate for bleeding ($p = 0.28$), stroke rate ($p = 0.90$), wound infection rate ($p = 0.96$), and length of mechanical ventilation ($p = 0.10$). This meta-analysis confirms that mini-sternotomy is a safe, feasible alternative option to full sternotomy in aortic root replacement. However, there is a need for a larger, well-designed trial to support the currently available limited evidence in the literature.

Conclusion

The mini-access approach described in this chapter allows the surgeon to perform not only aortic valve replacement, but also proximal aortic replacement or repair with reduced bleeding, post-operative pain, and reduced length-of-stay [15, 16]. The use of the left "J" mini-sternotomy facilitates full exposure of the proximal arch and aortic root, which is highly recommended by the authors. When a bio-prosthetic valve is to be used, the "French Cuff" technique provides excellent hemostasis in mini-access aortic surgery.

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Aortic Valve-Sparing Root Replacement

35

Mateo Marin-Cuartas and Michael A. Borger

High Yield Facts

- The term aortic valve-sparing root replacement (AVSRR) surgery encompasses a variety of techniques.
- The David operation or aortic valve implantation procedure is the most commonly performed AVSRR.
- Connective tissue disorders are usual etiologies of aortic root aneurysms in young patients.
- The David operation is particularly valuable in young patients and those with connective tissue disorders.
- Pliable aortic valve cusps are required for a successful performance of the David operation.
- Current guidelines recommend prophylactic aortic root/ascending aorta surgery in different scenarios in order to avoid aortic rupture or dissection.
- Outstanding short- and long-term survival as well as excellent freedom from reoperation have been demonstrated after the David operation.

Introduction

The term aortic valve-sparing root replacement (AVSRR) surgery encompasses a variety of techniques. The David operation or aortic valve reimplantation procedure is the most commonly performed AVSRR and was initially described by David and colleagues for the correction of aortic root aneurysms [1]. Numerous technical modifications of the David operation have been described over the years, with the most common forms being the David I procedure—using a straight tube graft—and the David V—using an oversized graft that is tailored at the subannular and sinotubular junction (STJ) levels (Fig. 35.1) [2]. Other variants of AVSRR include the remodeling or Yacoub technique [3], as well as modifications of the Yacoub procedure combined with a variety of aortic annuloplasty techniques [4–7].

AVSRR and the David operation can be performed in nearly all patients with aortic root aneurysms and pliable aortic valve cusps but are particularly valuable in young patients and those with connective tissue disorders. Outstanding short- and long-term survival as well as excellent freedom from reoperation have been demonstrated [1, 2, 8–10]. The current chapter will review the indications, techniques and outcomes for AVSRR, with a particular focus on the David operation.

Natural History

AVSRR is nearly always performed for aortic root aneurysm disease, although varying degrees of aortic regurgitation (AR) are addressed at the time of surgery.

Aortic dissection and rupture are the most feared complications of aortic root aneurysms, with an exponential increase in risk of these complications with increasing aortic diameter (Fig. 35.2) [11]. Patients with connective tissue disorders—and to a lesser degree bicuspid aortic valves—have an increased risk of aortic complications requiring lower thresholds for surgical intervention.

Pathophysiology

The aortic valve unit is composed of four structures, all of which need to be assessed when trying to understand the mechanism of AR in patients with aortic root aneurysms: the ventriculo-aortic junction (VAJ), the STJ, the aortic valve cusps, and the three sinuses of Valsalva (Fig. 35.3). The VAJ and the STJ together should be understood as the functional aortic annulus (FAA).

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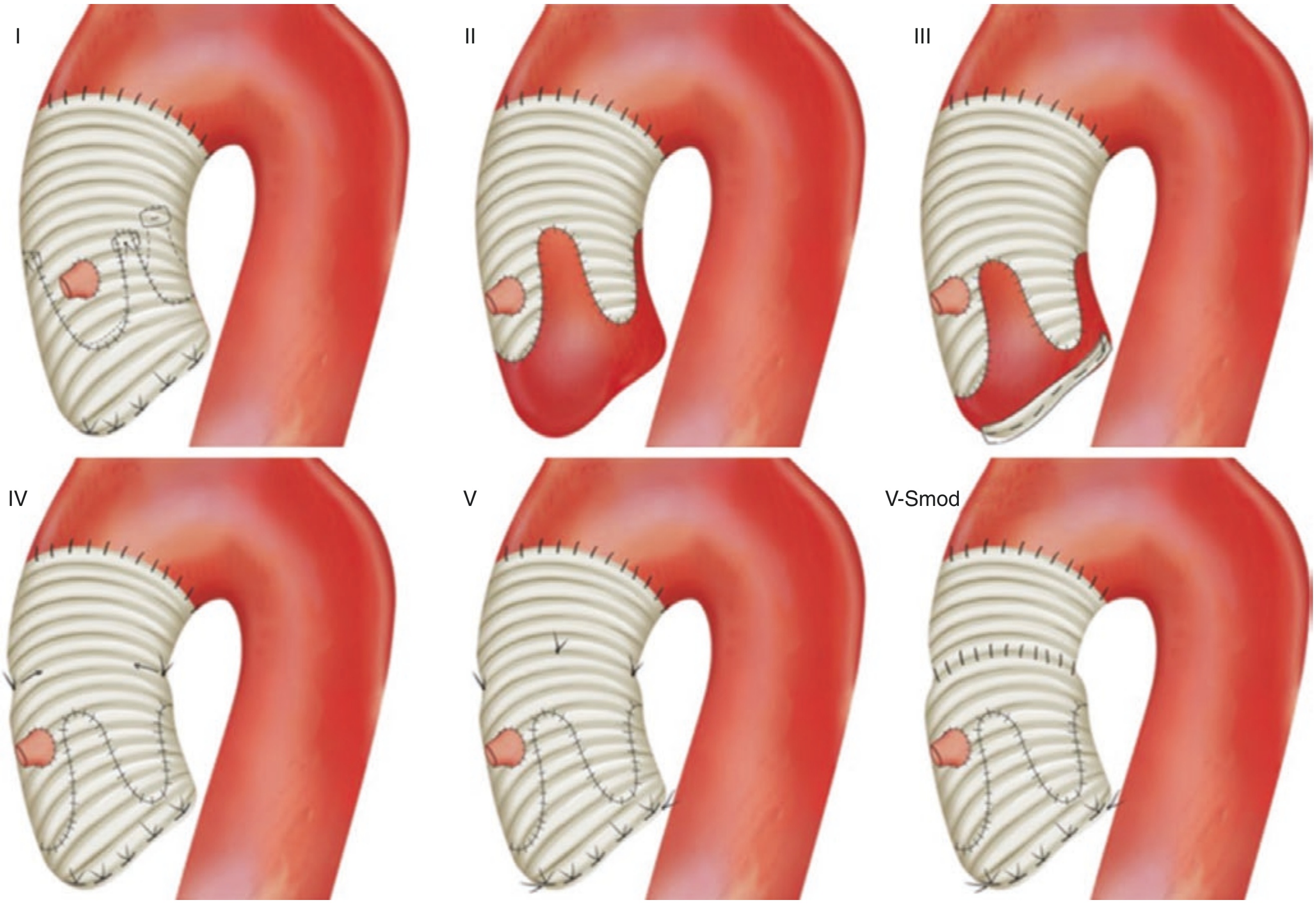
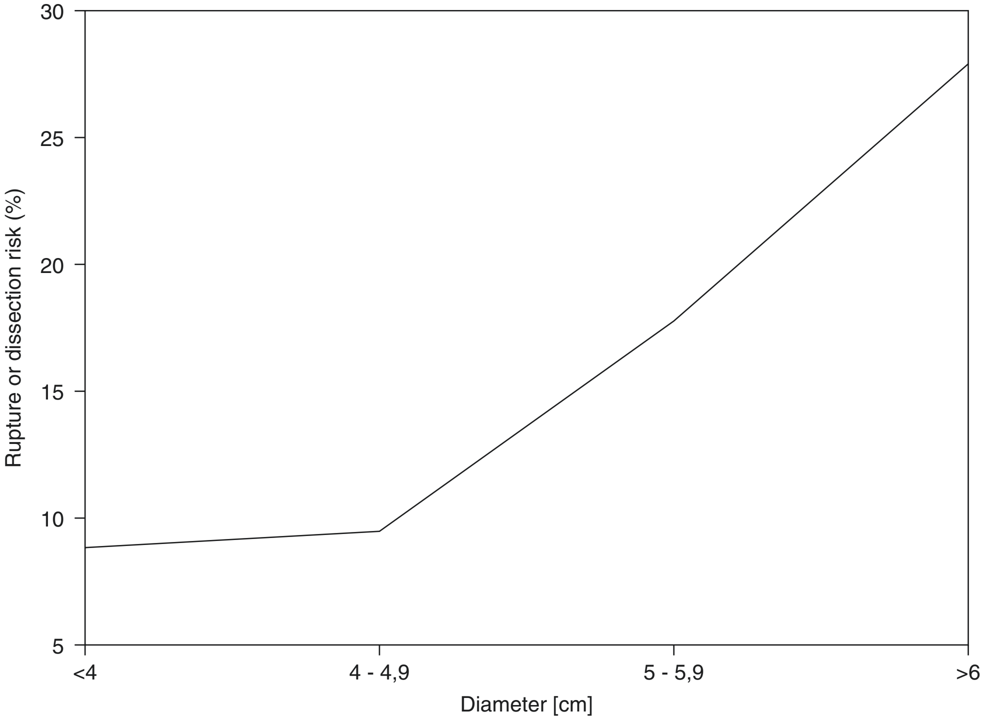


Fig. 35.1 Modifications of the David aortic valve-sparing root replacement procedure (Type I–V). “Smod” indicates Stanford modification. (Reproduced with permission from Kari et al. [2])

Fig. 35.2 Aortic rupture or dissection risk according to the aortic diameter along 30 months. (Modified from Coady et al. [11])



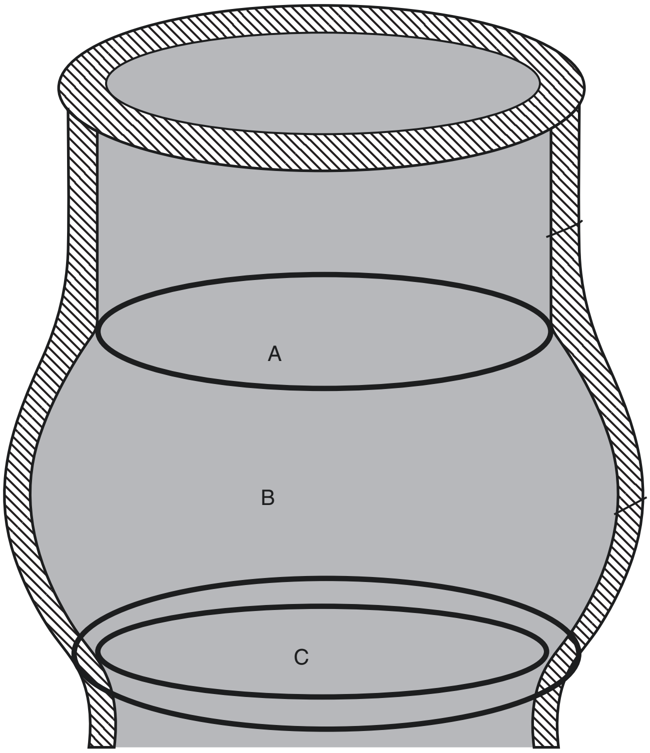


Fig. 35.3 Schematic representation of the aortic root. A = Sinotubular junction; B = Sinuses of Valsalva; C = Ventriculo-aortic junction. (Modified from De Kerchove L & El Khoury G. [9])

A close correlation between the progression of aortic root, STJ and VAJ diameters over time and AR severity has been shown [12, 13]. Aortic root aneurysms in patients older than 50 years occur as a consequence of a degenerative process which starts with dilatation of the ascending aorta and later progressing to dilatation of the STJ and aortic sinuses (beginning from the noncoronary sinus and then extending to the right and left coronary sinuses), but rarely affecting the VAJ and annulus. Supracoronary ascending aorta replacement and/or remodeling procedures are preferable for these patients.

In contrast, patients with connecting tissue disorders initially develop dilatation of the aortic sinuses, followed by the VAJ and STJ [14, 15]. Aortic root dilation leads to decreased AV cusp coaptation and subsequent AR [16]. However, other mechanisms of AR may be present and must be taken into consideration when planning the repair (Fig. 35.4) [17–20].

Connective Tissue Disorders

Marfan syndrome is an autosomal dominant inherited connective tissue disorders (CTD) with variable penetrance [21], with a reported incidence of 1 in 3000–5000 individuals [22]. The disease is caused by mutations of the gene that encodes fibrillin-1(FBN1) on chromosome 15 as well as an excess activation of transforming growth factor beta (TGF-ß). FBN1

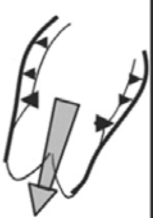
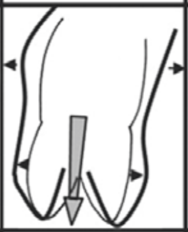
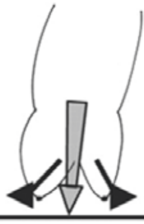
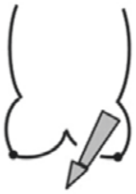
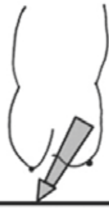
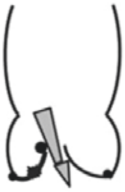
AI Class	Type I Normal cusp motion with FAA dilatation or cusp perforation				Type II Cusp Prolapse	Type III Cusp Restriction
	Ia	Ib	Ic	Id		
Mechanism						
Repair Techniques (Primary)	STJ remodeling *Ascending aortic graft*	Aortic Valve sparing: *Reimplantation or Remodeling with SCA*	SCA	Patch Repair *Autologous or bovine pericardium*	Prolapse Repair *Plication* *Triangular resection* *Free margin Resuspension* *Patch*	Leaflet Repair *Shaving* *Decalcificatio* *Patch*
(Secondary)	SCA		STJ Annuloplasty	SCA	SCA	SCA

Fig. 35.4 Functional repair-oriented aortic regurgitation classification. *AI* aortic incompetence, *FAA* functional aortic annulus, *SCA* subcommissural annuloplasty, *STJ* sinotubular junction. (Reproduced with permission from De Kerchove L. & El Khoury G. [9])

mutations are responsible for a weaker extracellular matrix and TGF-ß abnormal activity leads to activation of metalloproteinases, inflammatory responses and fibrosis [23, 24]. This causes aortic medial degeneration which leads to loss of elasticity and distensibility, resulting in a progressive dilatation of the aortic root and predisposing to aortic dissections.

Loeys-Dietz syndrome occurs due to mutations in the genes encoding the TGF-ß receptors 1 and 2. This disease can present with a wide spectrum of clinical manifestations. In the most severe forms, aortic dissection and rupture can occur in early childhood even at relatively small diameters and are associated with generalized arterial tortuosity and widespread vascular aneurysms [25].

Ehlers-Danlos is a more uncommon autosomal dominant inherited CTD caused by a mutation of the gene encoding for type III collagen. It is characterized by spontaneous rupture of the abdominal aorta and other great caliber arteries at young age. Aortic dissection is uncommon and less than 30% of the patients have aortic root dilatation [26]. Diagnosis is confirmed with biochemical assays and molecular biology studies.

Indications and Patient Selection

The traditional indication for AVSRR surgery is aortic root aneurysm with or without AR. Acute type A aortic dissection is also an indication for AVSRR, but only in experienced hands and in select patients [27, 28]. Current guidelines recommend prophylactic aortic root/ascending aorta surgery in the following scenarios [29, 30]:

1. Aortic root disease irrespective of the severity of AR with maximal ascending aortic diameter:
   (a) >45 mm in the presence of Marfan syndrome and additional risk factors or patients with a TGFBR1 or TGFBR2 mutation (including Loeys–Dietz syndrome). (Recommendation IIa C)
   (b) >50 mm in the presence of a bicuspid valve with additional risk factors (AR, uncontrolled hypertension, aortic growth >3 mm/year or family history of dissection). (Recommendation IIa C)
   (c) >50 mm and Marfan syndrome without risk factors. (Recommendation I C)
   (d) >55 mm for all other patients. (Recommendation IIa C)
2. Severe AR as primary indication for aortic root/ascending aorta surgery:
   (a) Aortic root or ascending aorta >45 mm particularly in the presence of a bicuspid valve. (Recommendation IIa C)

Several factors should be considered when deciding whether or not to perform an AVSRR procedure (Table 35.1). Pliable, mobile, non-calcified aortic cusps are of utmost importance for a successful AVSRR procedure with or without additional aortic valve repair. Small cusp fenestrations located adjacent to the commissures do not need to be addressed. Type I (enlargement of the aortic root with normal cusp motion) or type II (cusp prolapse) mechanisms of AR (Fig. 35.4) are most appropriate for a repair [19, 20, 31]. Most CTD patients with aortic aneurysms meet these characteristics. However, a massively dilated aortic root may preclude successful repair due to overstretched cusps with multiple fenestrations.

Table 35.1 Factors influencing decision of whether or not to perform David procedure

In favor	Against
Young patient	Aortic valve calcification
AR secondary to dilatation of the FAA	Age >70 years
Hemodynamically stable AAD	Type III mechanism of AR
Pliable, smooth non-calcified cusps	Very large aortic root aneurysm
Types I and II mechanisms of AR	Multiple cusp fenestrations
	Need for concomitant cardiac surgery
	Inexperienced surgeon

AR aortic regurgitation, *FAA* functional aortic annulus, *AAD* type A aortic dissection

AVSRR is more likely to be successful when performed by an experienced aortic surgeon, preferably at a high volume center [32]. Most failures appear to be related to technical errors [33].

Remodeling of the Aortic Root and Other Annuloplasty Techniques

Together with the aortic valve reimplantation procedure (David operation), remodeling of the aortic root or Yacoub operation is another variant of AVSRR [3]. However, in patients with annuloaortic ectasia and aortic root aneurysm due to genetic syndromes, remodeling of the aortic root may be inappropriate as the aortic annulus tends to further dilate postoperatively [34]. Nevertheless, Lansac et al. demonstrated the value of external aortic ring annuloplasty to provide a reproducible technique for aortic valve repair with satisfactory long-term results [6]. Schäfers et al. have also demonstrated very good results for the remodeling procedure combined with VAJ annuloplasty [4, 5]. Both of these groups have demonstrated feasibility of this technique in a wide variety of pathologies, including bicuspid or tricuspid aortic valves [6]. However, the majority of surgeons perform the David reimplantation procedure and this is our AVSRR procedure of choice.

Aortic cusp prolapse is frequently encountered during AVSRR surgery. Cusp prolapse may exist as an isolated pathology of the aortic valve, it can coexist with root dilatation, or it may even be induced by reduction of root diameters after AVSRR [35]. Its repair still remains a challenge to surgical judgment, since assessment of pathology and evaluation of repair results are very difficult due to the complex 3-dimentional anatomy of the aortic root and the limitations of standard imaging tools such as echocardiography. Prolapse of one cusp can be easily recognized by comparing the prolapsing cusp with the other two healthy cusps. However, prolapse of two or three cusps is more difficult to assess and treat, because of lack of reference cusp for comparison. Schäfers et al. observed that repaired valves that resulted in low aortic cusps effective height were associated with recurrent AR and reoperation. These investigators recommended intraoperative measurement of the effective cusp height as a useful guide to quantify cusp prolapse and assess the results of valve-preserving surgery. An effective height of 8 mm or more is a predictor of low recurrent AR [4]. The standardized employment of calibrated expansible aortic ring annuloplasty together with the assessment of cusp effective height improves valve repair outcomes for patients with a dilated annulus (>25 mm) undergoing aortic root remodeling procedures [7].

The David Operation

The remainder of this chapter focuses on the technicial description of the David operation, since this is the AVSRR procedure of choice in our center and the majority of aortic surgery centers. Patients are operated through a midline sternotomy, although a upper hemi-sternotomy may be employed in select patients. Options for arterial cannulation include the distal ascending aorta, aortic arch, brachiocephalic trunk, or axillary artery depending on the aneurysm extent. The right atrium is cannulated with a double-stage cannula, and the left ventricle is vented through the right superior pulmonary vein. We prefer to give antegrade blood cardioplegia directly into the coronary ostia, although some surgeons prefer retrograde delivery via the coronary sinus. Following cardioplegic arrest and aortotomy, close inspection of the valvular apparatus is performed in order to confirm the pathology. Thereafter, the operation is performed following the original description by David and Feindel [1].

The three aortic sinuses are excised, while carefully mobilizing the coronary buttons. Dissection is carried down deep around the aortic root, until the entire VAJ is mobilized. The aortopulmonary fibrous band must be completely divided and the right ventricular outflow tract mobilized away from the VAJ. Inadequate mobilization of the VAJ can result in tethering of the annulus and adjacent aortic valve cusp with subsequent AR.

Pledgeted 4-0 polypropylene sutures are then placed a few millimeters above each commissure and all three commissures are pulled up vertically (i.e. towards the operating room roof) (Fig. 35.5). The optimal annular and STJ diameter is then determined by measuring the distance that results in optimal aortic valve cusp coaptation (Fig. 35.6). The optimal annular and STJ diameters range from 24 to 30 mm in most patients (Fig. 35.7). We prefere to use a straight Dacron tube graft for the David operation, although commercially

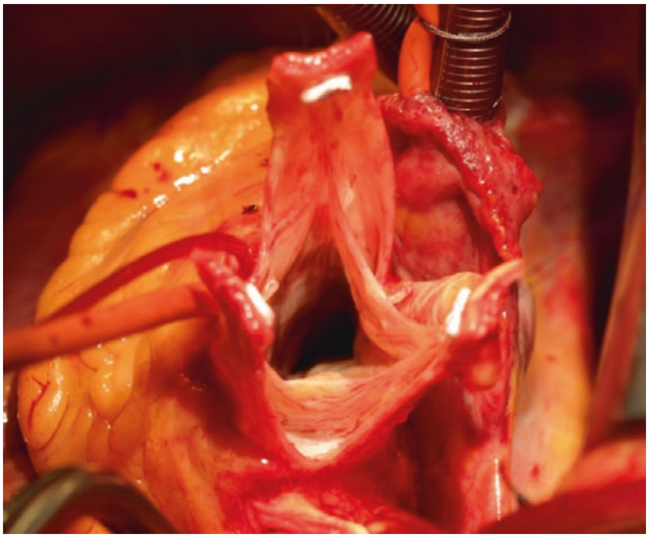


Fig. 35.5 Excised aortic sinuses. Commissures are pulled upwards to confirm complete mobilization of the entire valve apparatus

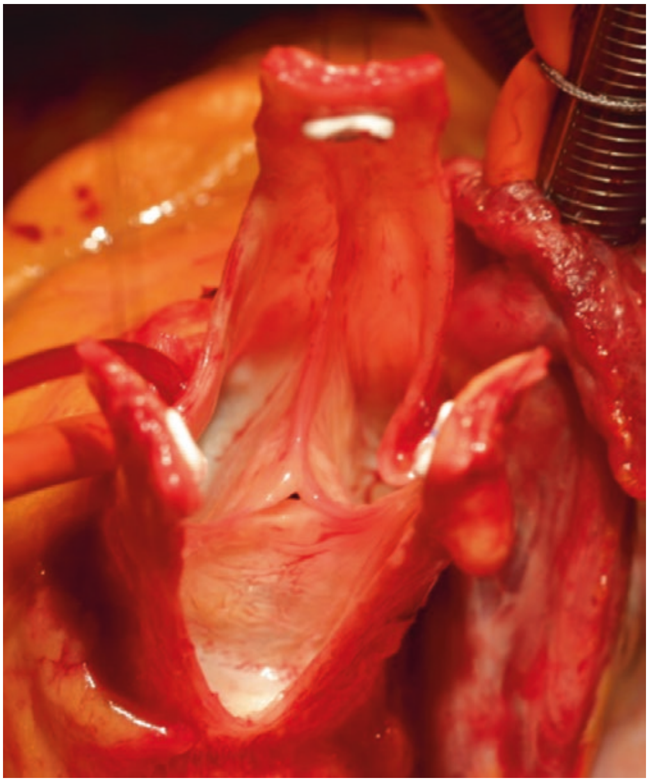


Fig. 35.6 Optimal aortic valve cusp coaptation

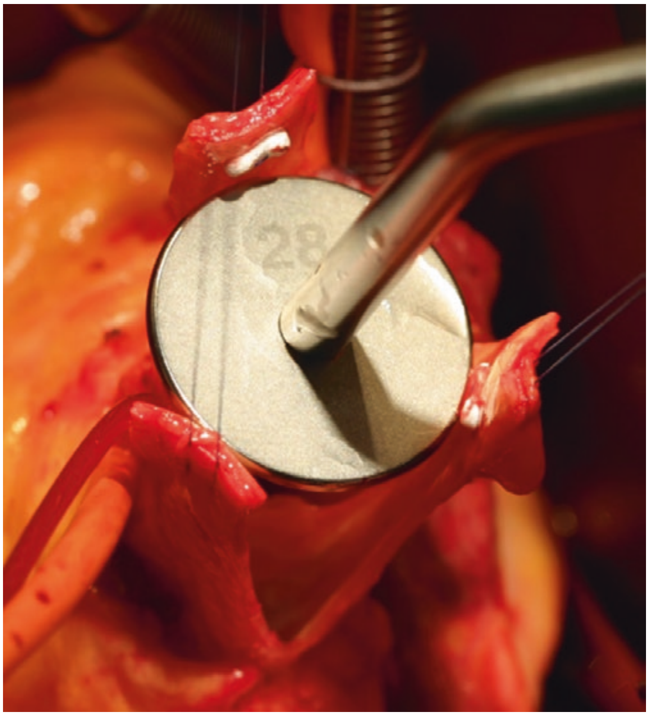


Fig. 35.7 Sizing of the sinotubular diameter that results in optimal cusp coaptation, which is then used for Dacron graft selection (see text)

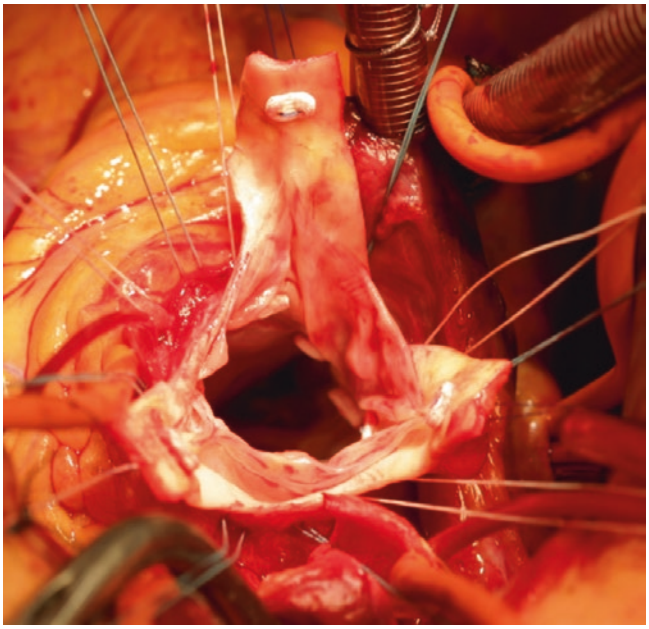


Fig. 35.8 Multiple horinzontal-matress polyester sutures passed from the inside to the outside of the left ventricular outflow tract, inmediately below the nadir of the aortic annulus

available grafts with neo-sinuses are prefered by many others. If a David I operation is being performed, then the optimal STJ diameter is the same as the chosen Dacron graft. If a David V operation is planned, then a 4–6 mm larger Dacron graft than the measured optimal annular diameter is selected. Other sizing techniques have been described in the literature, but we believe the above technique is the simplest and most reproducible.

Multiple horinzontal matress sutures of 2-0 or 3-0 polyester are then passed from the inside to the outside of the left ventricular outflow tract (LVOT), inmediately below the nadir of the aortic annulus (Fig. 35.8). The sutures are placed in a single horizontal plane, with the exception of the subcommisural triangle between the right and noncoronary cusps. Here the sutures are passed in a scalloped form through the membranous septum in order to avoid the bundle of His. Teflon pledgeds are used for the fibrous portion of the LVOT, but are not required for the muscular portion. Properly placed sutures through the LVOT and Dacron graft may be used to result in annular plication at the subcommisural triangles of the noncoronary aortic cusp in patients with marked annular dilation, since this is where the annular dilation tends to occur.

Three equidistant “commissural” marks are placed on the inflow portion of the Dacron graft, in order to help with orientation. A small triangular segment may be trimmed from the Dacron graft in the area corresponding to the subcommisural triangle of the left and right cusps. If performing a David V operation, the proximal end of the graft is plicated with three polypropylene 5-0 sutures between the commisural marks (Fig. 35.9).

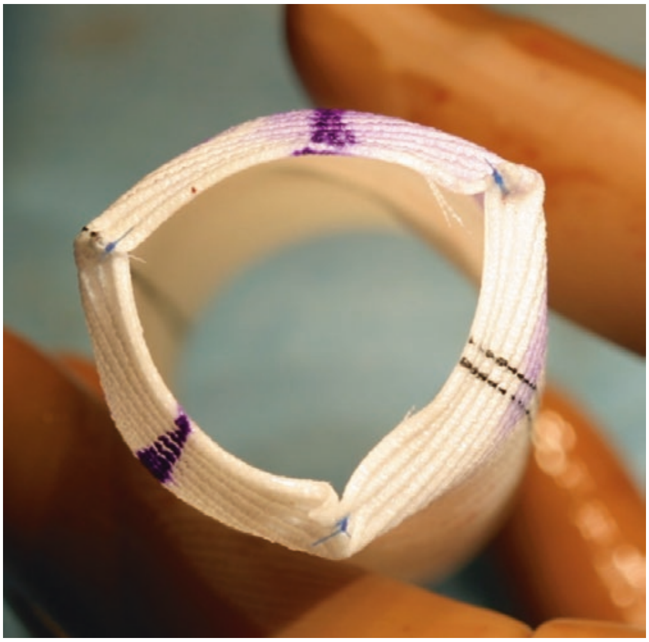


Fig. 35.9 Plication of the proximal end of the Dacron graft between the commisural marks to create neoarotic sinuses during David V procedure

The sutures previously placed in the outflow tract are now passed through the Dacron graft, approximately 5 mm from its free edge. The sutures are then carefully tied on the out-

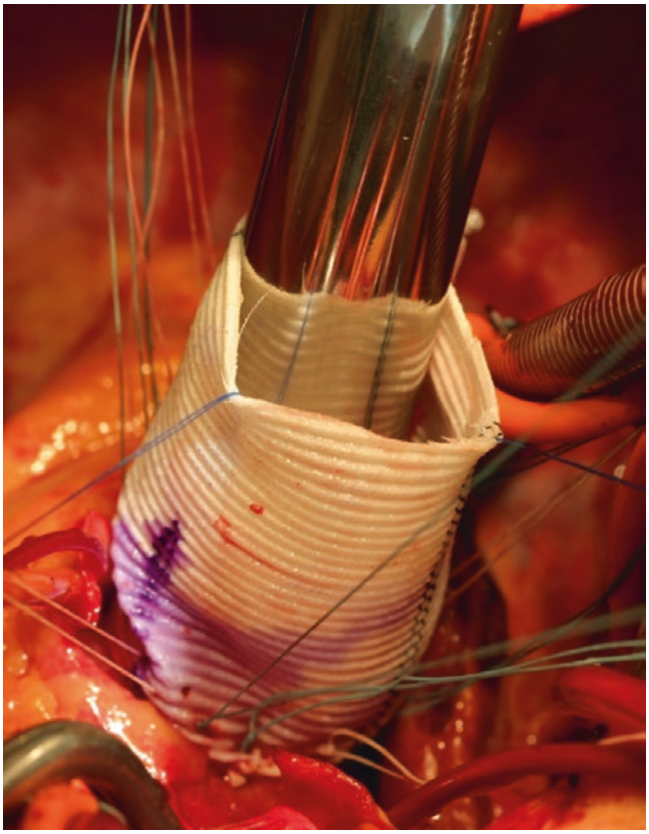


Fig. 35.10 Subannular sutures are passed through the graft and carefully tied on the outside of the graft. A 22 or 23 mm Hagar dilator may be placed through the valve prior to tying the sutures

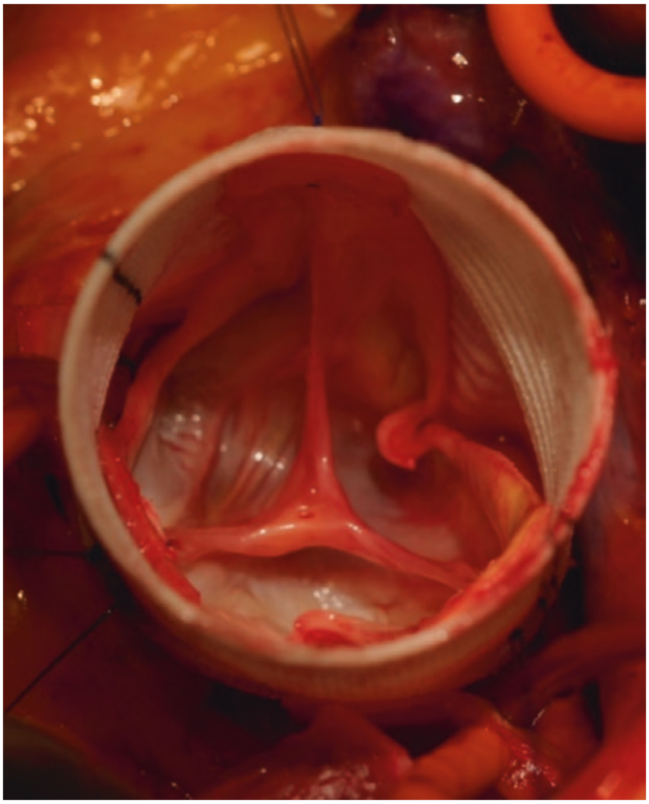


Fig. 35.11 Commissural positioning for optimal cusp orientation and coaptation

side of the graft, ensuring that the entire annulus is contained within the graft. A 22 mm Hegar dilator may be inserted through the annulus before tying these sutures, in order to avoid excessive tension resulting in a purse-string effect and valvular distortion (Fig. 35.10). It should be stressed that this suture line is not intended to be hemostatic. The Dacron graft is usually cut to be approximately 5 cm in length in order to facilitate performance of the next suture line, which ***must*** be hemostatic. Gentle vertical traction is placed on the graft (i.e. pulled vertically towards the operating room ceiling) while the 4-0 polypropylene sutures are temporarily secured to the graft buttressed on small teflon pledgeds. The commissures should be positioned rather high within the graft in order to narrow the subcommissural triangles, particularly in patients with bicuspid aortc valves. The polypropylene sutures are not tied until the correct position is found for all three commisures, resulting in optimal cusp orientation and coaptation (Fig. 35.11). The commisures and the cusps are therefore carefully inspected to ensure optimal positioning and cusp coaptation, with repositioning of the commissural sutures as required. Cusp coaptation level should be central and well above the VAJ (i.e. effective height >8 mm). The polypropylene sutures are then sewn to the aortic annulus/aortic wall remnants. We prefer to use a horizontal suturing method for this suture line, but a running suture is also acceptable. Gentle upward traction should be applied to the commissures when performing this suture line, in order to obtain good alignment of the annulus with the adjacent Dacron graft.

Once the aortic annulus is fixed to the Dacron graft, a water test is performed prior to implantation of the coronary arteries to confirm valve competency (Fig. 35.12). Vertical traction of the Dacron graft is required during the water test. If the water level falls during upward traction of the Dacron graft, the cusps must be re-examined for possible malcoaptation or distortion. The effective height is also examined at this time. Cusp prolapse is usually corrected with central plication using a 5-0 polypropylene suture. Fenestrations near the commisures can be ignored, but large central fenestrations need to be repaired with 5-0 Gore-Tex suture (W.L. Gore, Flagstaff, AZ). A detailed description of other cusp repair techniques is provided in the chapter on aortic valve repair (Chap. 39). Cusp restriction or distortion (usually caused by improperly placed annular and subannular sutures) are particularly difficult problems to correct, and may require aortic valve replacement at this time.

Next, the coronary ostia are reimplanted into the respective sinuses of the Dacron graft with 5-0 polypropylene sutures. Felt reinforcement is not required for these suture lines. If a

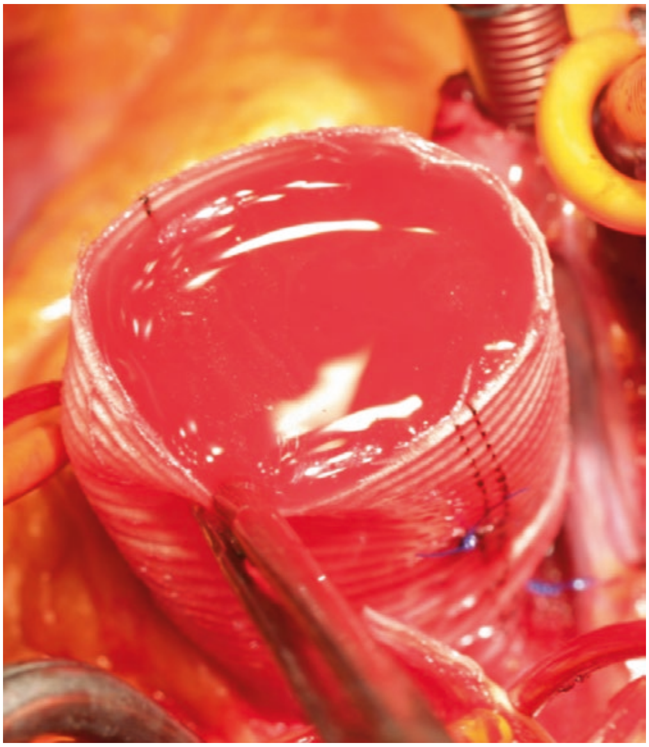


Fig. 35.12 Water sealing test

David V operation is being performed, creation of neoarotic sinuses is now performed by plicating the graft at the level of the STJ halfway between the commisures, using a 5-0 polypropylene. Valve competency may now be reconfirmed by clamping the distal end of the graft and injecting water under pressure. Absense of left ventricular distention means no more than trace aortic regurgitation. The distal graft anastomosis is now performed to the ascending aorta or to a second Dacron graft, according to the extent of the pathology.

Results

Excellent early- and long-term results have been described for elective AVSRR surgery [8, 36–41]. In addition, patients with connective tissue disorders like Marfan or Loeys-Dietz syndromes, or even more challenging situations such as bicuspid aortic valve or acute type A aortic dissection, have also been demonstrated to have very satisfactory outcomes with AVSRR [15, 42, 43]. Several centers have demonstrated an early mortality rate of zero percent for elective AVSRR patients [10, 32, 44]. Different groups have reported a 2-year survival rate >95% [8, 36, 37, 45, 46]. A total of 179 patients undergoing AVSRR in our center between 2003 and 2011 showed an early mortality rate of 1.1% [10]. When patients with acute type A aortic dissection were excluded, there was no mortality. The predischarge echocardiography revealed trace-to-mild AR in 19.6% of patients, and no AR in 80.4% of patients. Left ventricular end-diastolic diameters decreased significantly from 5.6 ± 0.9 to 5.1 ± 0.8 cm early postoperatively ($p < 0.01$), and AR grade remained less than moderate in 93.6% of patients during follow-up. Five-year freedom from aortic valve reoperation was 95.9 ± 2.0% [10]. After 18 years follow-up, David et al. demonstrated a survival rate of 76.8%, which is only 10% less than that of the matched general population [8]. The same series showed a freedom from moderate-to-severe AR of 78% and a freedom from reoperation of 94.8% after 18 years. Similarly good results have been demonstrated in patients with bicuspid aortic valve disease when compared to those with tricuspid aortic valves [33, 41].

Very good outcomes in patients undergoing surgery for acute aortic dissection have also been demonstrated in select centers [27, 28, 46–48]. Long-term survival and freedom from aortic valve reoperation in patients surviving the initial hospitalization is similar to non-acute aortic dissection patients who undergo the David procedure [47].

Conclusion

It has been more than two decades since aortic valve-sparing operations were introduced to preserve the aortic valve in patients with aortic root aneurysm. Remodeling of the aortic root is physiologically superior to reimplantation of the aortic valve, mainly because it preserves the aortic annulus motion during the cardiac cycle. However, several comparative studies have shown that reimplantation of the aortic valve provides more stable aortic valve function than remodeling of the aortic root. This difference in outcomes is largely because of patients' selection. Remodeling of the aortic root has been associated with high failure rates in patients with aneurysms associated with genetic syndromes and bicuspid aortic valves with dilated aortic annulus, but it has provided excellent long-term results in older patients with aortic root dilation secondary to ascending aortic aneurysms and normal aortic annulus. Thus, both techniques are useful in preserving the aortic valve. With either technique, restoration of normal aortic annulus and cusp geometry is the single most important technical aspect of these operations. In addition to having a competent valve with no or trivial AR at the end of the operation, there must be no cusp prolapse and the coaptation level of the cusps has to be well above the level of the nadir of the aortic annulus.

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36

Aortic Valve Repair

Igo B. Ribeiro and Munir Boodhwani

High Yield Facts

- Aortic valve repair has evolved to improve the complication rates of valve-related events commonly seen in surgical bioprostheses, namely reoperation, structural valve deterioration, endocarditis, bleeding and thromboembolic events.
- The comprehension of the functional aortic annulus (sinotubular junction and ventriculo-aortic junction) and its interaction with the aortic cusps allowed for the understanding of the mechanism of insufficiency and the development of surgical techniques to correct specific anatomical abnormalities.
- The repair-oriented functional classification of aortic insufficiency has allowed for better communication of the mechanism of the disease among physicians and surgeons alike and provided a roadmap that integrates anatomy, valve function and surgical technique.
- Aortic valve repair has low operative mortality with overall survival and valve-related survival at 10 years of 75% and 90%, respectively.
- Freedom from reoperation and from aortic insufficiency ≥2+, varies between 85–95% at 10 years in selected and unselected series.
- Linearized risk of endocarditis, thromboembolism, and bleeding is less than 0.5%-year for each.
- Aortic valve repair seems a better alternative to a surgical prosthesis for selected candidates with aortic root aneurysm and aortic insufficiency.

Introduction

Aortic valve repair has emerged as an attractive surgical alternative treatment for aortic valve insufficiency. Although aortic valve replacement is still considered the gold standard of surgical treatment for aortic valve disease, aortic valve repair has demonstrated superior outcomes in centres of excellence [1–3]. Prosthetic valves are far from an ideal solution for aortic valve disease. Concerns regarding durability of the biological valves, the need for life-long anticoagulation for mechanical prostheses, potential poor hemodynamic performance, and life-long prosthesis-related complications are some of the risks related to the surgical valves.

Since the introduction of the concept of aortic valve-sparing operation for the surgical treatment of root aneurysms by David and Yacoub in the late 1980s, interest in the surgical preservation of aortic valve has increased. The indications of aortic valve repair have expanded to include non-aneurysmal aortic valve insufficiency with the development of surgical techniques for cusp repair [4, 5]. A better understanding of aortic valve pathophysiology led to the creation of a repair-oriented classification of aortic valve insufficiency [6] that guides the use of specific surgical techniques to address aortic valve abnormalities [4, 7, 8]. Follow-up data beyond the first decade has demonstrated good repair durability and low risk of valve-related complications with aortic valve repair [1–3, 9]. This trend has similarities to what was observed for mitral valve repair surgery, which is at present the standard of care for degenerative mitral valve insufficiency.

In this chapter, we review the key features of the functional aortic valve anatomy, the indications of aortic valve repair, intra-operative valve assessment and classification, review of surgical aortic valve repair techniques and outcomes.

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Aortic Root Anatomy

Functional Aortic Annulus

The understanding of the anatomy and interaction of the aortic annulus components with the leaflets has been the key to the development of aortic valve repair techniques. The function of the aortic valve requires a complex interaction of multiple components of the aortic root to allow for coaptation of the aortic cusps, avoiding aortic regurgitation. Figure 36.1 demonstrates the components of the aortic root, namely the sinotubular junction (STJ), the ventriculo-aortic junction (VAJ) or basal annulus, the sinus of Valsalva (SOV), the interleaflet triangles and the crown-shaped insertion of the cusps [10]. Each cusp meets the adjacent cusp at its most distal insertion point, called commissure. The plane connecting the three commissure forms the sinutubular junction (STJ). The basal ring is an oval structure formed by the plane connecting the nadir of each aortic cusp. This structure lies in the left ventricle outflow tract (LVOT). The transition between the aortic tissue and the ventricular muscle is often referred to as the VAJ. This point is typically a few millimeters higher than the basal ring and can vary based on the location along the aortic valve. The interleaflet triangles are delineated by two adjacent cusp insertion and the basal annulus. The SOVs are outpouching aortic wall structures that are demarcated by the insertion of each cusp [10]. The right and left coronary arteries originate in the SOV. In a tricuspid aortic valve, each cusp is named after the coronary artery that takes off from the SOV, namely right coronary cusp (RCC), left coronary cusp (LCC) and non-coronary cusp (NCC) (Fig. 36.2) [11]. The STJ and the VAJ work together with the

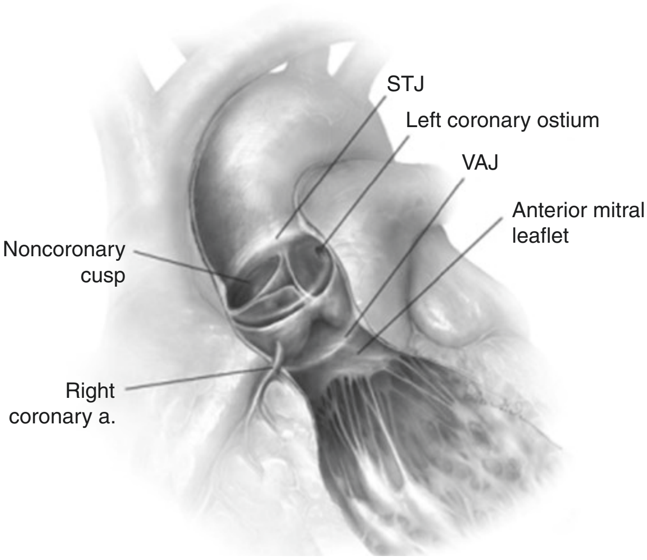

STJ
Left coronary ostium
VAJ
Anterior mitral leaflet
Noncoronary cusp
Right coronary a.

Fig. 36.2 Anatomy of the aortic valve and the functional aortic annulus. *STJ* sinotubular junction, *VAJ* ventriculo-aortic junction. (From Boodhwani M, El Khoury G. Aortic Valve Repair. Operative Techniques in Thoracic and Cardiovascular Surgery 2009;14:266–80, with permission)

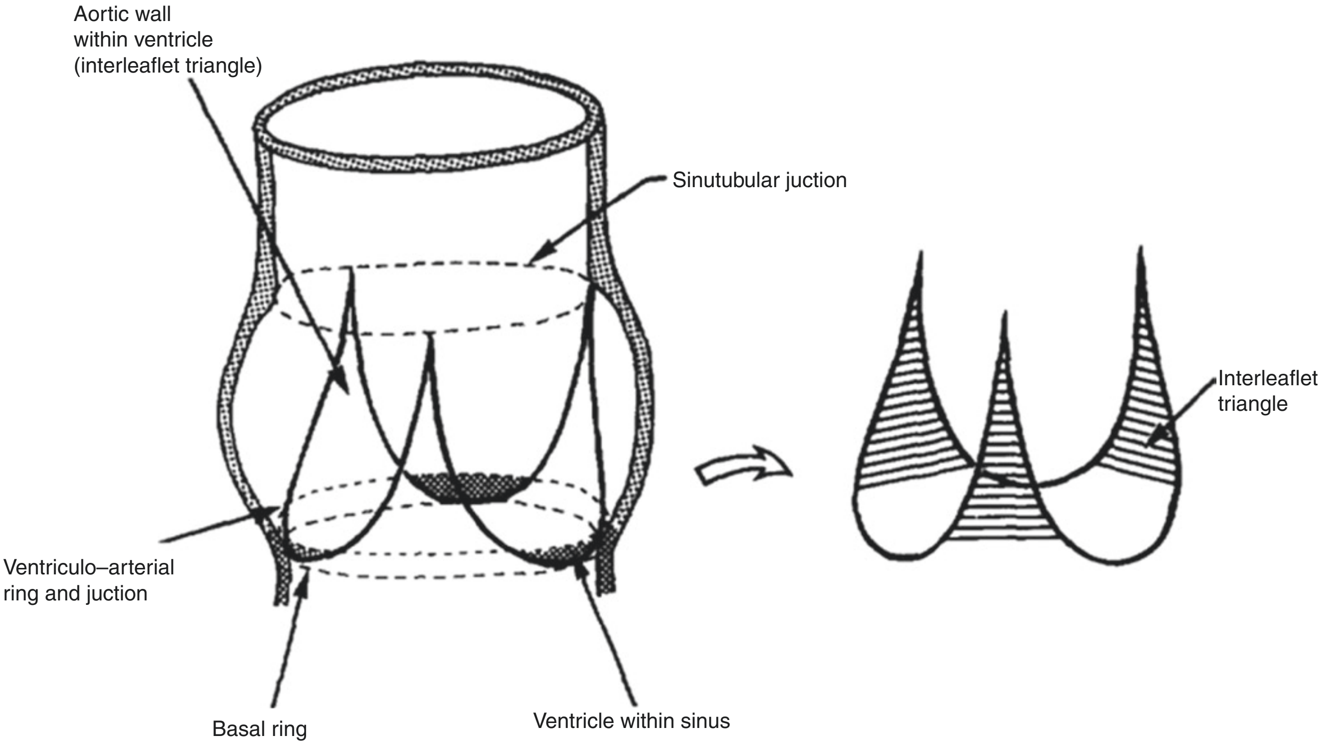

Aortic wall within ventricle (interleaflet triangle)
Sinutubular juction
Interleaflet triangle
Ventriculo–arterial ring and juction
Basal ring
Ventricle within sinus

Fig. 36.1 Diagrammatic representation of the aortic root. (From Sutton III JP, Ho SY, Anderson RH. The forgotten interleaflet triangles: A review of the surgical anatomy of the aortic valve. Ann Thorac Surg 1995;59:419–27, with permission)

valve cusps to assure the normal functioning of the aortic valve, and together they are termed the functional aortic annulus (FAA). Any disruption of any components of the FAA may lead to aortic insufficiency.

Some important anatomical parameters of the aortic root and aortic valve have critical implications for both aortic valve repair and long-term outcomes of a repaired valve. In a normal aortic valve, the aortic valve cusp dimensions correlate to the anatomy of the FAA, i.e., larger FAA requires bigger cusps. Some parameters that describe cusp anatomy and function are the cusp geometric height, the aortic valve effective height, the coaptation height and the commissure height. First, the geometric height is the distance between the nadir of the cusp and its free margin at its center. It is measured in systole and easily performed in the operating room during cardioplegic arrest and root assessment. Schafers and colleagues [12] demonstrated that in tricuspid aortic valves the geometric height of the non-coronary cusp is statistically greater than the left and right aortic cusps, with the mean size of 20.7 ± 2.2 mm. In this study, the geometric height of the right and left aortic cusp was similar (20 ± 2.1 mm). The cusps size correlated to age, sex, body surface area, VAJ dimension [12]. The authors suggested that geometric cusp height equal to or less than 16 mm in the tricuspid aortic valve and 19 mm in the non-fused cusp of a bicuspid aortic valve should be considered restricted and not ideal for repair. The second important parameter is the cusp effective height which is the orthogonal distance from the VAJ to the tip of the coaptation line at the center of the cusp. It is measured in diastole with the valve in closed position with a dedicated caliper [12]. On echocardiography, it can be measured in the long axis view of the aortic valve. The normal range is 7–12 mm [13]. The coaptation length is the length of the cusp apposition in diastole. This value has prognostic implication for repair durability with a length less than 5 mm associated with increased recurrent aortic insufficiency. Lastly, the commissural height is the distance from the annular plane to the top of the commissure. Based on the principle that the commissure heights correlate to the STJ, De Kerchove and colleagues demonstrated that the height of the N/L commissure is equal to the external STJ diameter and easily measured intraoperatively. Therefore, the authors suggest this measurement is an easy method for graft size selection during valve-sparing root replacement. Figure 36.3 depicts all the measured parameter of the aortic root and aortic valve cusps [14].

In another study, De Kerchove and colleagues [15] analyzed 58 aortic roots specimens from which they demonstrated that the aortic root is asymmetrical with important implication for aortic valve reparative surgery. For instance, the internal root height is asymmetrical. The height of the L/R commissure is slightly smaller than the N/L and N/R commissures. Also, they demonstrated that the normal basal ring diameter is 22.6 ± 2.6 mm. More importantly, this study demonstrated that there is a height difference between the level of the external VAJ after maximal root dissection (not entering into the right ventricular muscle) and the level of the internal VAJ (basal annulus). The level of maximal external dissection does not match the level of the basal annulus (internal VAJ) from the L/R commissure, along with the right coronary sinus and the N/R commissure. The height difference in the internal height was 4.6 ± 1.4 mm, 2.4 ± 1.5 mm and 2.5 ± 1.6 mm at the L/R commissure, along with the right coronary sinus and at the N/R commissure, respectively. Therefore, surgical techniques that aim at stabilizing the VAJ require the understanding of this anatomical limitation of external dissection. The anatomical limiting structures are the RV ventricular mass at the L/R commissure

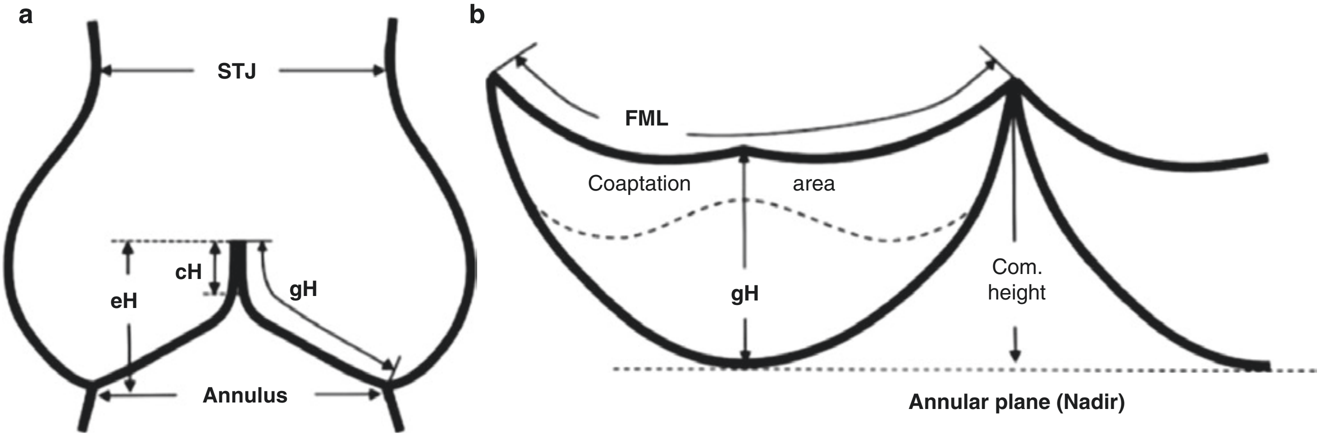


Fig. 36.3 Diagram of aortic valve and root illustrating the different anatomical measurements used in aortic valve repair. *cH* coaptation height (**a**), *Com. height* commissure height (**b**), *eH* effective height (**a**), *FML* free margin length (**b**), *gH* geometric height (**a** and **b**), *STJ* sinotubular junction diameter (**a**). (From Lansec E, de Kerchove L. Aortic valve repair techniques: state of the art. Eur J Cardiothoracic Surg, 2018;53:1101–1107, with permission)

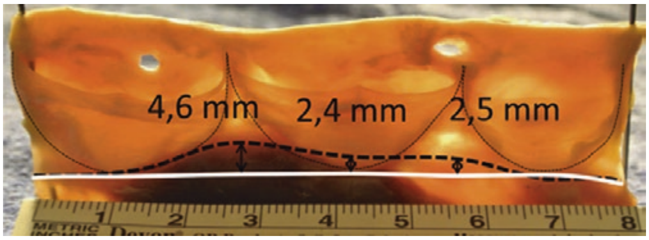


Fig. 36.4 Relationship between the internal basal annulus (white) to the external VAJ maximal dissection (dashed blackline). (From de Kerchove L, Jashari R, Boodhwani M, Duy KT, Lengelé B, Gianello P, et al. Surgical anatomy of the aortic root: implication for valve-sparing reimplantation and aortic valve annuloplasty. J Thorac Cardiovasc Surg 2015;149:425–33, with permission)

and along the RC cusp and the membranous septum at the N/R commissure. Deep sutures placement at the VAJ near the N/R commissure may impinge the Bundle of His causing complete heart block. Figure 36.4 demonstrates the distance of external dissection of the VAJ to the inner annulus.

Indications for Aortic Valve Repair

Decision-making for aortic valve preserving or repair surgery requires the consideration of surgical indications of either aortic valve insufficiency or aneurysmal disease of the aorta. According to the 2017 European Society of Cardiology (ESC) and European Association of Cardiothoracic Surgery (EACTS) guidelines, aortic valve repair is a class I indication for the treatment of aortic regurgitation in selected patients with pliable non-calcified tricuspid and bicuspid aortic valve as well as for aortic root and tubular ascending aortic aneurysm [16].

Table 36.1 shows the surgical indications for aortic valve regurgitation and aortic root pathology according to the 2017 ESC/EACTS guidelines.

Table 36.1 Surgical indications for aortic valve regurgitation and aortic root pathology

Indication for surgery	Class	Level of evidence
Aortic regurgitation		
Symptomatic patients	I	B
Asymptomatic patients with resting EF <50%	I	B
Surgery is indicated patient undergoing CABG or surgery of aorta or another valve	I	C
Asymptomatic patients with resting ejection fraction >50% with severe LV dilation: LVEDD >70 mm or LVESD >50 mm or indexed LVESD >25 mm/m^2 patients with small body size	2A	C
Aortic root or tubular ascending aortic aneurysms		
Marfan's patient with aortic root or ascending aorta size ≥50 mm	1	C
Surgery should be considered in patients with aortic disease and maximum aortic diameter of: • >45 mm in Marfan syndrome and risk factors[a] or patients with TGFBR1 or 2 mutations (including Loeys-Dietz syndrome[b]) • >50 mm in the presence of bicuspid aortic valve and risk factor or coarctation • >55 for all other patients	2A	C
When surgery is primarily indicated for aortic valve, replacement of aortic valve or ascending aorta should be considered if diameter ≥45 mm, particularly in the presence of bicuspid aortic valve.	2A	C

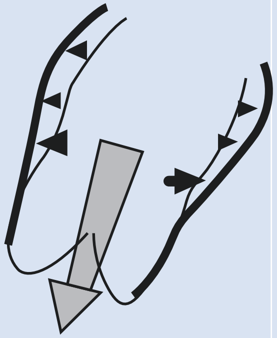
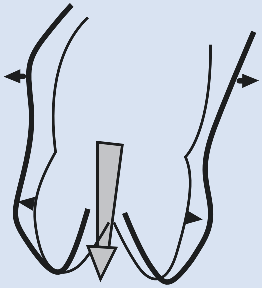
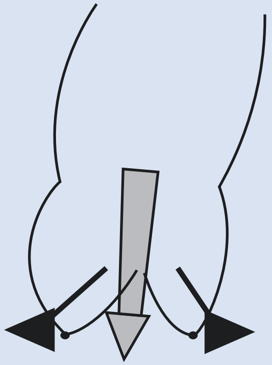
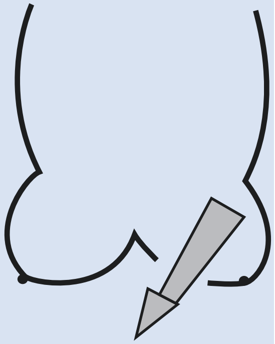
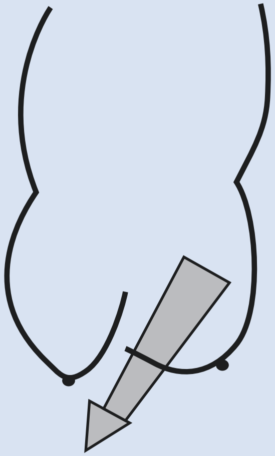
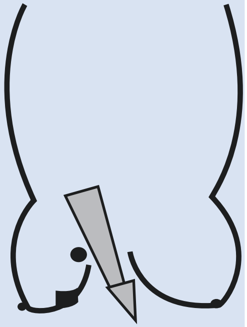
[a] Family history of aortic dissection (or personal history of spontaneous vascular dissection), severe aortic regurgitation or mitral regurgitation, desire for pregnancy, systemic hypertension and/or aortic size increase >3 mm/year

[b] A lower threshold of 40 mm may be considered in women with low BSA, in patients with a TGFBR2 mutation or in patients with severe extra-aortic features

Assessment of Aortic Valve and the Repair-Oriented Classification

The development of the repair-oriented functional classification of aortic valve insufficiency has led to a better understanding of the mechanisms of insufficiency, which improved communication among cardiac surgeons, cardiologists, and anesthesiologists [6]. This classification correlates anatomical anomalies to the mechanism of the disease and sheds light on the possible repair techniques to correct each anatomical abnormality. Similar to the widespread Carpentier's classification for mitral valve disease, the aortic valve classification is based on the motion of aortic cusps, keeping in mind that the functional aortic annulus has two unique components. Aortic insufficiency that has a normal cusp motion is referred to as type 1. The mechanism of insufficiency is largely due to a lesion of the functional aortic annulus. Type 1a insufficiency is due to lack of apposition of the aortic cusp due to dilation of the STJ and ascending aorta. This type of regurgitation causes a central regurgitant jet in the LVOT. Type 1b also causes central regurgitation due to dilation of both STJ, the sinuses of Valsalva, and the VAJ, typically seen in aortic root aneurysms. Type 1c is a pure dilation of the VAJ, which also cause lack of cusp apposition and central regurgitation. Type 1d is mostly seen in the context of infective endocarditis. The cusps have normal motion, but there is cusp perforation, which leads to a central or oblique regurgitant jet. Type 2 aortic regurgitation is caused by excess motion of the cusps, causing prolapse of one or more aortic cusps. This is secondary to excess of tissue (increased cusp free margin) or commissure disruption. The regurgitant jet is eccentric, away from the prolapsing cusp. Type 3 aortic regurgitation is due to decreased cusp motion, causing cusp restriction. The regurgitant jet is also eccentric and typically directed towards the restricted cusp. This entity can be found in rheumatic valve disease, bicuspid aortic valves or degenerative aortic valve disease due to calcification of the aortic cusps. The repair-oriented functional classification is illustrated in Table 36.2.

Table 36.2 Repair-oriented functional classification of aortic insufficiency (AI) with description of disease mechanisms and repair techniques used

AI class	Type 1 Normal cusp motion with FAA dilatation or cusp perforation				Type II cusp prolapse	Type III cusp restriction
	Ia	Ib	Ic	Id		
Mechanism						
Repair techniques (Primary)	STJ remodeling *Ascending aortic graft*	Aortic valve sparing: *Reimplantation or remodeling with SCA*	SCA *External circumferential ring*	Patch repair *Autologous or bovine pericardium*	Prolapse repair *Plication triangular resection free margin resuspension patch*	Leaflet repair *Shaving decalcificatio patch*
(Secondary)	SCA		STJ Annuloplasty	SCA	SCA *External circumferential ring*	SCA *External circumferential ring*

FAA functional aortic annulus, *STJ* sinotubular junction, *SCA* subcommissural annuloplasty. (Modified from Boodhwani M, de Kerchove L, Glineur D, Poncelet A, Rubay J, Astarci P, et al. Repair-oriented classification of aortic insufficiency: impact on surgical techniques and clinical outcomes. J Thorac Cardiovasc Surg 2009;137:286–94, with permission)

Surgical Techniques

Standard midline sternotomy and heart preparation are generally performed for aortic valve repair. Arterial cannulation site varies depending on the need of ascending aorta or arch replacement. Ascending aorta cannulation for arterial inflow for cardiopulmonary bypass suffices for most cases without arch pathology. Arch or axillary cannulation are alternative sites when ascending aorta, or hemiarch replacement is required. A single two-stage venous cannulation is inserted into the right atrium as well as a left ventricular vent into the right superior pulmonary vein. Cardioplegic arrest is performed.

Valve Exposure and Assessment

A transverse aortotomy is performed approximately 1 cm above the STJ. A 2–3 cm posterior aortic wall is left intact as part of the exposure strategy. A full-thickness 4-0 polypropylene suture is placed in the distal aorta and retracted cephalad. This maneuver helps in pulling up the aortic annulus upwards. Next, a full-thickness 4-0 polypropylene suture is placed at each commissure. These three sutures are of paramount importance as part of the assessment of the aortic valve. Figure 36.5 demonstrates the aortic valve exposure. Next, the valve is visually assessed. Fibrosis, calcification, perforation, restriction, and prolapse are possible issues. Interestingly, a prolapsed cusp will often demonstrate a transverse fibrous band, which corresponds to the cusp bending over itself during diastole. Besides visual assessment, quantitative measurements such as the effective and geometric height can be performed. These measurements help to clarify cusp prolapse or restriction.

Restoration of the Functional Aortic Annulus

The repair-oriented classification guides the surgical treatment of each lesion. Type 1a lesions are corrected by reconstruction of the STJ. This is performed by replacing the ascending aorta, substituting it with a Dacron graft with the size of the desired STJ dimension. Different methods can be used to choose the Dacron graft size [17]. First, the polypropylene sutures at each commissure are pulled axially and centrally until optimal coaptation of the leaflets is obtained; then a valve sizer is utilized to measure the new diameter of the STJ (Fig. 36.6). Graft oversizing should be avoided as it can lead to central aortic regurgitation (Type 1a lesion). In cases of significant aortic insufficiency, subcommissural annuloplasty (SCA) may be performed to remodel the VAJ which will increase the cusps coaptation length. Type 1b lesions are frequently seen in root aneurysms. These lesions are frequently associated with dilatation of both STJ and VAJ. Therefore, valve-sparing root replacement using the reimplantation technique as described by David and Feindel [18] should be the pre-

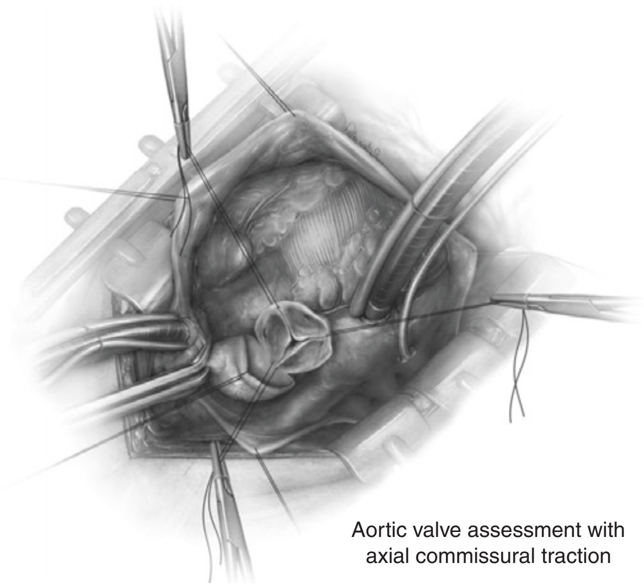


Fig. 36.5 Exposure of the aortic valve through a transverse aortotomy. (From Boodhwani M, El Khoury G. Aortic Valve Repair. Operative Techniques in Thoracic and Cardiovascular Surgery 2009;14:266–80, with permission)

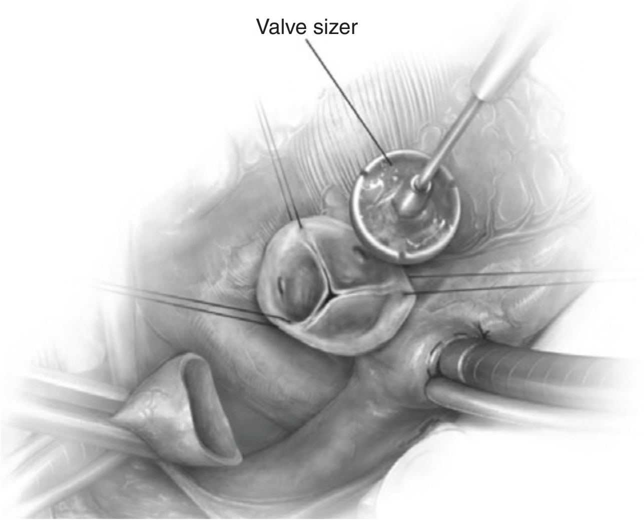


Fig. 36.6 Sizing of aortic prosthesis. Traction is applied to the commissural retraction sutures to place the valve in physiologic closing position with adequate cusp coaptation. The sinotubular junction is sized in this position. Oversizing the prosthesis can lead to central regurgitation, whereas undersizing can induce cusp prolapse. (From Boodhwani M, El Khoury G. Aortic Valve Repair. Operative Techniques in Thoracic and Cardiovascular Surgery 2009;14:266–80, with permission)

ferred method of repair. This technique allows for a more durable stabilization of both STJ and VAJ [18]. Remodeling technique as proposed by Yacoub et al. [19] may be used to treat root aneurysms, but this technique should be left for those patients whose VAJ dilation is unlikely to occur. If remodelling procedures are performed, a VAJ annuloplasty should be added. Type 1c lesions requires remodeling of the VAJ. Therefore, SCA or external circumferential ring annuloplasty are potential solutions.

Subcommissural Annuloplasty

Subcommissural annuloplasty (SCA) (Fig. 36.7) also known as Cabrol stitch [20] remodels the VAJ by decreasing the width of the interleaflet triangles. It is usually performed at the middle of each triangle by placing a pledgeted 2-0 braided suture at each side of the triangle. Lower suture placement can be performed if greater increase of coaptation length is required. However, at the N/R commissure, deep suture placement should be avoided since it may damage the membranous septum or cause heart block. Although the SCA increases the coaptation length by increasing the effective cusp height and help stabilize the VAJ, complete annular stabilization is not achieved. This is important for bicuspid aortic valve as SCA alone rarely prevents future dilation. SCA is not appropriate for large annulus (>28–30 mm) [21–23]. In this context, VAJ circumferential ring annuloplasty as an adjunct repair has been proposed as a more robust VAJ stabilization technique [24].

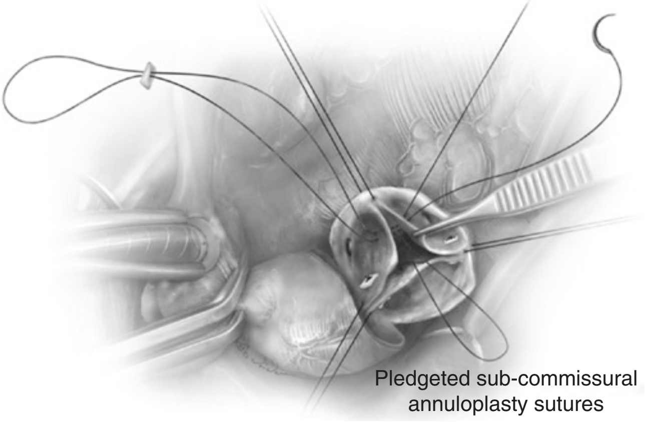


Fig. 36.7 The first arm of the suture is passed from the aortic to the ventricular side, in the interleaflet triangle, and comes back out to the aortic side at the same level. The second arm of the suture is passed in a similar fashion just below the first. A free pledget is added and the suture is tied. This maneuver helps to stabilize the ventriculo-aortic junction, reduces the width of the interleaflet triangles, and increases the coaptation surface of the valve leaflets. (From Boodhwani M, El Khoury G. Aortic Valve Repair. Operative Techniques in Thoracic and Cardiovascular Surgery 2009;14:266–80, with permission)

Valve-Sparing Root Replacement: Reimplantation Technique

Valve-sparing root replacement using the reimplantation technique provides the most stable annuloplasty of the VAJ. Recently, 20 years of follow-up data have supported the long-term durability of the reimplantation technique [25, 26]. Besides the treatment of aortic root aneurysm in tricuspid aortic valves, this technique also provides stability for bicuspid valve repair, where progressive annulus dilation is a common feature. The keys steps are outlined below.

- *External aortic root dissection*: The root is dissected circumferentially as proximal as possible. Usually, the dissection starts at the NC cusp. At the NC cusp, the dissection usually can be carried out below the valvular plane. The right ventricular muscle and the membranous septum limits the dissection of the aortic root along the area between L/R and the N/R commissure. Deep external root dissection along the right coronary cusp may reach the level of the internal VAJ. However, de Kerchove and colleagues showed that this maneuver requires partially dissection of the RV wall to reach the internal level of the VAJ [15].
- *Sinus of Valsalva resection and coronary buttons preparation*: All three sinuses of Valsalva are resected. Both coronary ostia are harvested, leaving a 5–7 mm of the rim of the aortic wall around each coronary ostium. This facilitates coronary reimplantation and avoids ostial stenosis. Also, a 3–5 mm rim of aortic wall is left attached to the aortic annulus to allow the reattachment of the aortic valve into the Dacron tube graft.
- *Dacron graft selection*: Straight tube grafts or those with built-in neoaortic sinuses can be used. Most recently, we have used the N/L subcommissural height as the method of choice to select the graft size. A surgical ruler is used to perform this measurement. This is based on the principle that the external STJ diameter is equal to the height of the interleaflet triangle (Fig. 36.8). Although aortic root components may dilate, the height of the commissures is relatively constant. The graft is marked where the new commissure should be reimplanted. In a tricuspid aortic valve, the cusp orientation is mostly 120°. However, some commissural adjustments are occasionally needed due to cusp asymmetry. Three dots are made on the graft height that corresponds to each commissure.
- *Graft preparation and valve re-implantation:* For the proximal suture line, 2-0 polyester pledgeted sutures are placed in the basal ring at the level of the nadir of the NC cusp along the fibrous part of the annulus. Given the external limitation of the root dissection along the muscular part as demonstrated by de Kerchove et al. [15], a

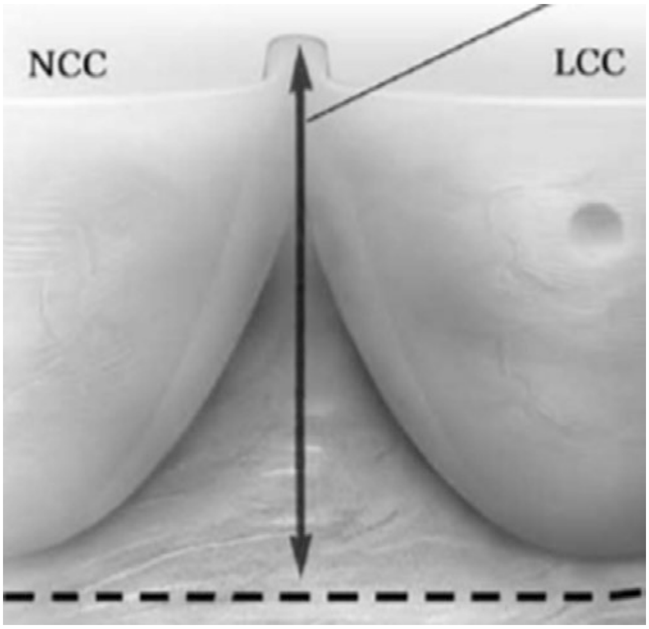


Fig. 36.8 The height of the N/L commissure is a reliable intra-operative measurement to choose the ideal graft size. (From de Kerchove L, Boodhwani M, Glineur D, Noirhomme P, El Khoury G. A new simple and objective method for graft sizing in valve-sparing root replacement using the reimplantation technique. Ann Thorac Surg 2011;92:749–51, with permission)

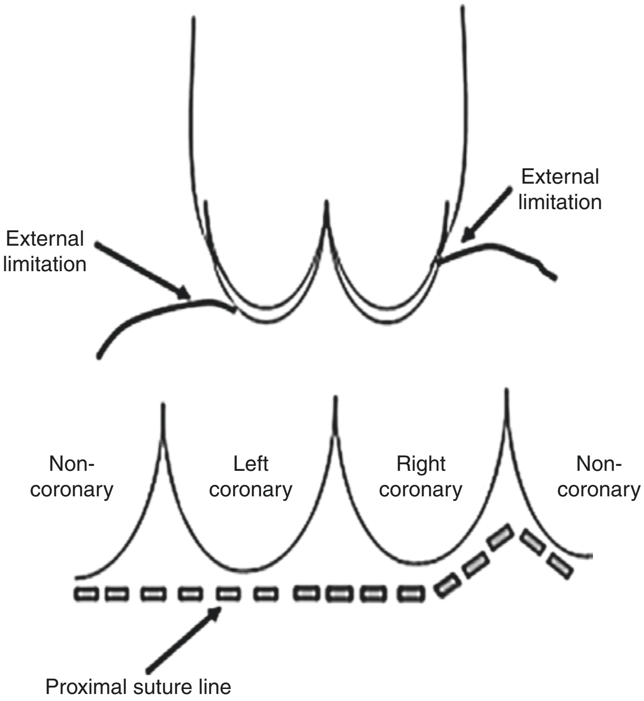


Fig. 36.9 Diagram demonstrating the proximal suture line. (Modified from Boodhwani M, de Kerchove L, El Khoury G. Aortic root replacement using the reimplantation technique: tips and tricks. Interact Cardiovasc Thorac Surg 2009;8:584–6, with permission)

deep external muscular dissection should be performed which allows placement of the proximal pledgeted suture line along the basal ring at the muscular septum. Due to the membranous septum limitation and the risk of damaging the conduction system, the proximal pledgeted suture line should take a course slightly higher following the crown-shaped cusp insertions at the N/R commissure [27] (Fig. 36.9). This avoids not only the conduction system but also excessive tension on the proximal suture line. Next, the graft is tailored. At the N/R commissure, the graft is tailored based on the difference of the internal and external height of the commissure (Fig. 36.10). The remainder of the graft remains horizontal. The 2-0 polyester sutures are placed circumferentially at the base of the new graft. The three commissural 4-0 polypropylenes that were used to exposure and to dissect the aortic root are passed inside the tube graft, allowing the aortic cusps to sit inside the graft. The graft is parachuted down, and all polyesters sutures are tied. Each commissure is attached to the graft at the height of the new STJ using the 4-0 polypropylene (the same used for valve exposure). The built-in neoaortic sinuses graft facilitates this step as the STJ is already pre-formed. For straight tube grafts, the surgeon selects the correct place of the new STJ based on the height of the N/L commissure. Once the three commissures are in place, the aortic cusps are reimplanted onto the Dacron graft wall by the three 4-0 polypropylene running sutures. Suture bites are performed through the outside of the graft into the 3–5 mm rim of the aortic wall, then back from inside to outside the graft. This running suture is performed by small bites all around the crown-shaped rim very close to the cusp insertion. Attention should be taken to avoid any cusp injury.

- *Leaflet assessment and repair:* After the valve implantation into the graft, assessment of valve coaptation is key to examine for leaflet pathology and function. A stepwise approach is useful. First, pressurization of the aortic root to assess for ventricular distention and aortic valve closure is performed. The tube graft can be pressurized using cardioplegia. Lack of ventricular distension is one sign of the absence of significant aortic insufficiency. Also, limited echocardiographic view can be obtained during this maneuver. Step two consists of valve inspection in its closed position by aspirating the residual blood on the top of the aortic valve without distorting it. This allows for assessment of prolapse, the height of coaptation and cusps apposition asymmetry. Third, quantitative measurements can be taken with the aortic valve repair dedicated caliper should doubts arise. After the cusp assessment, cusp reparative technique is implemented as needed. The coronary buttons are then reimplanted, and the distal anastomosis is performed.

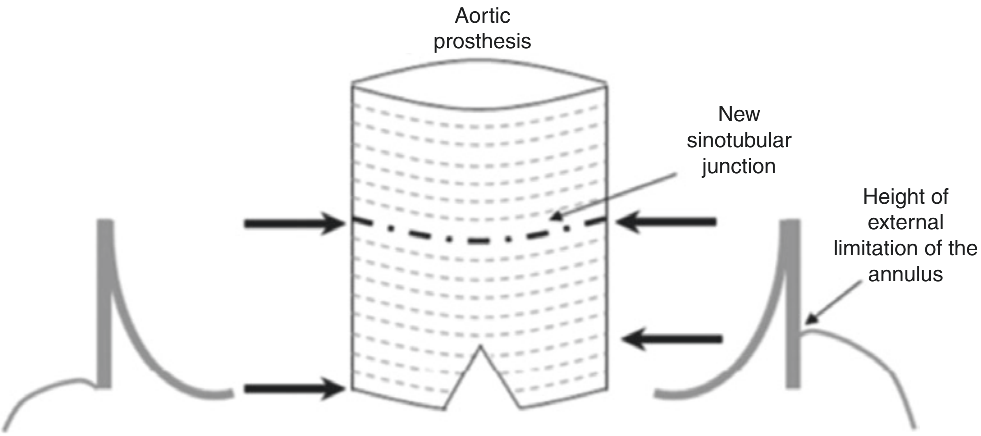


Fig. 36.10 Diagram showing prosthesis preparation. (From Boodhwani M, de Kerchove L, El Khoury G. Aortic root replacement using the reimplantation technique: tips and tricks. Interact Cardiovasc Thorac Surg 2009;8:584–6, with permission)

Aortic Valve Annuloplasty

The concept of aortic annuloplasty was first described by Tayler and colleagues using a technique called circumclusion in 1958 [28]. Most recently, aortic circumferential annuloplasty has emerged again as a method for annular reduction and stabilization. The annuloplasties can be performed at the VAJ and the STJ level. Lansac and colleagues have developed an expansible ring that can be used as an adjunct to a remodelling procedure. Alternative materials include a Dacron band of appropriate size or other flexible annuloplasty materials like the SimpliciT band (Medtronic Inc., MN, USA). This technique is mostly used as an adjunct to the remodeling technique during valve-sparing root replacement or stabilization of a moderate dilated aortic annulus in Type 1c lesions. This technique also faces the same challenge of limited external dissection of the aortic root. Internal aortic annuloplasties are also under various stages of development and evaluation [29, 30].

Cusp Repair Techniques

Cusp quality is critical for reparative aortic valve surgery. Cusp prolapse is the most common cusp pathology involved in aortic sufficiency. This is caused by excess length of the free margin. Degenerative disease or longstanding aortic insufficiency can stretch the cusps causing cusp fenestrations and commissural disruption. Cusp prolapse occurs when the effective height decreases making the cusp bend over itself creating the fibrous band commonly seen during echocardiographic and surgical examination. The correction of cusp effective height aims at allowing the three cusps to coapt at the midpoint of the aortic root. Rarely, all cusps prolapse. If so, the middle of the aortic root should be the reference point for cusp height correction. In most cases, a non-prolapsing cusp should be the reference point for the height correction of the prolapsing one. Central free margin plication and free margin resuspension are the two techniques that address aortic cusp prolapse [4].

- *Free margin plication*: A 6-0 polypropylene suture is placed at the nodule of Arantius of the two non-prolapsing cusps (in the mid of the cusp). This suture serves as the reference stitch. This 6-0 polypropylene is pulled axially under minor tension to mimic the closed position of both leaflets. Then, the margin of the prolapsing cusp is pulled parallel to the free margin of the non-prolapsing cusp. Next, a 6-0 polypropylene is passed from the aortic side to the ventricular side at the free margin where it meets the reference point. Then, the same prolapsing cusp is pulled the other way, stretching the other half of the free margin. Again, where the free margin meets the reference point, the same suture is passed from the ventricular side to the aortic side. The length of the free margin between the two arms of the polypropylene suture corresponds to the excess free margin length. The free margin is plicated by tying this suture. The plication is extended 5–10 mm onto the body of the cusp using either a running or locking technique. If there is extensive tissue, parsimonious cusp shaving, or triangular resection may be performed, keeping enough tissue to restore the cusp. Figure 36.11 depicts the free margin plication technique.
- *Free margin resuspension*: Excess free margin can be shortened by reinforcing the free margin using a 7-0 PTFE suture and adjusting the length accordingly. A 7-0 PTFE suture is placed from outside the aorta into the commissure of the prolapsing cusp and passed over and over along the free margin until it reaches the other commissure. Another 7-0 polypropylene is passed from outside the aorta and run over and over the free margin until it reaches the other commissure. From one side of the cusp, the two sutures outside the aorta are tied and

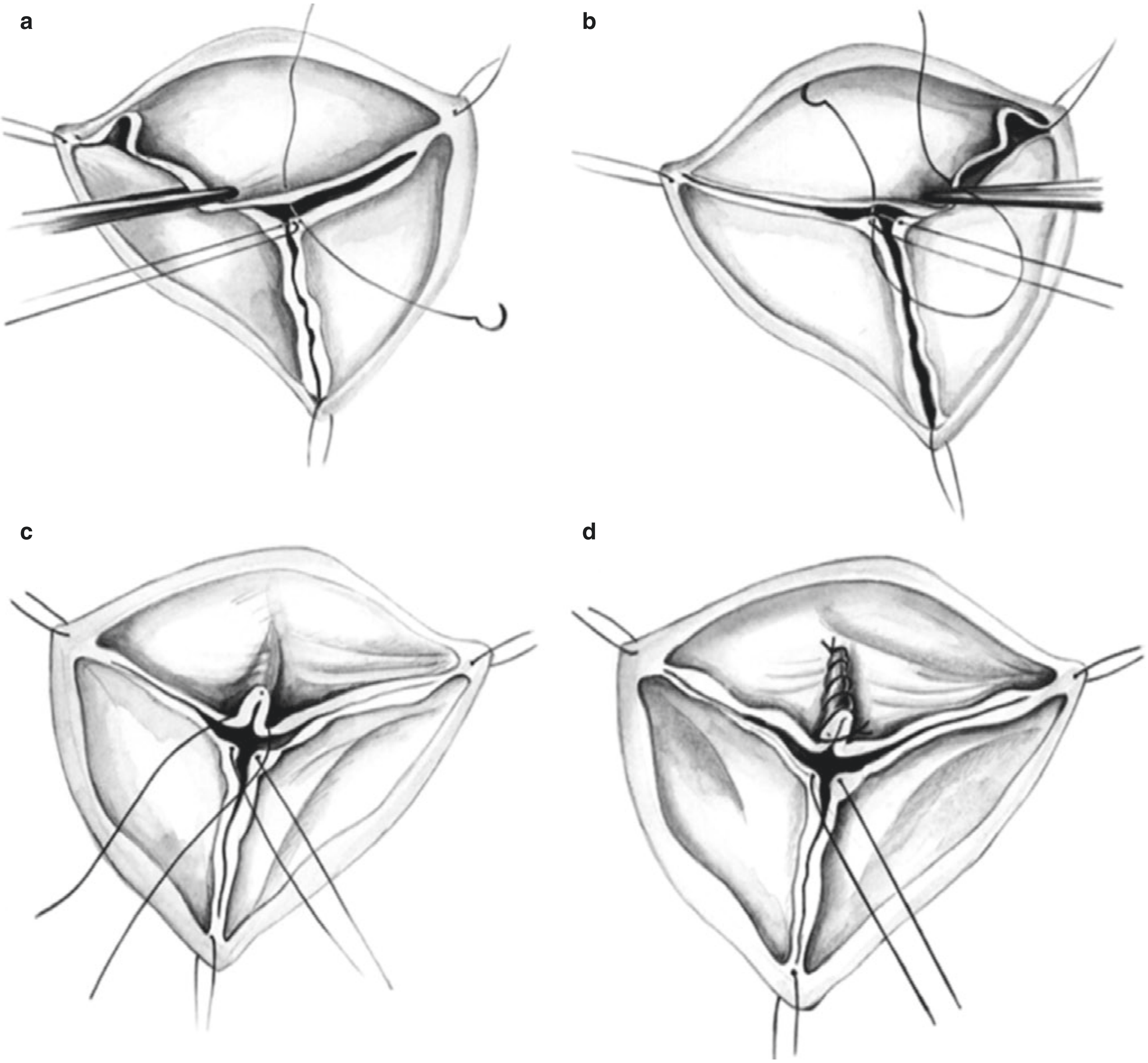


Fig. 36.11 The four steps of free margin plication technique. (**a**) Traction of the prolapsing leaflet to meet the reference point. A 7-0 polypropylene is placed at this point. (**b**) Reverse traction. The same polypropylene is placed at the free margin where it meets the reference point. (**c**) Polypropylene is tied on the aorta side. (**d**) Leaflet plication is extended to 5–10 mm onto the body of the cusp. (From Boodhwani M, El Khoury G. Aortic Valve Repair. Operative Techniques in Thoracic and Cardiovascular Surgery 2009;14:266–80, with permission)

locked. Gentle axial tension is applied on the prolapsing cusp until it reaches the reference point (nodule of Arantius of the non-prolapsing cusps). Then, the other arms of the PTFE suture are gently pulled to imbricate the free margin, shortening it accordingly. The other ends of the two 7-0 PTFE are passed outside the aorta and tied together (Fig. 36.12). This technique is particularly useful for cusps with multiple fenestration and commissural disruption because it homogenizes the free margin.

Bicuspid Valve Repair

Bicuspid aortic valve (BAV) disease affects 1–2% of the general population. Eventually, 20% of this population develops significant aortic insufficiency [31]. Young adults develop more aortic insufficiency and have more root aneurysms compared to the elderly patients that often present with aortic stenosis and an enlarged ascending aorta. Different phenotypes affect the bicuspid aortic valve. Sievers et al. [32] have demonstrated the most bicuspid aortic valve have an asymmetric con-

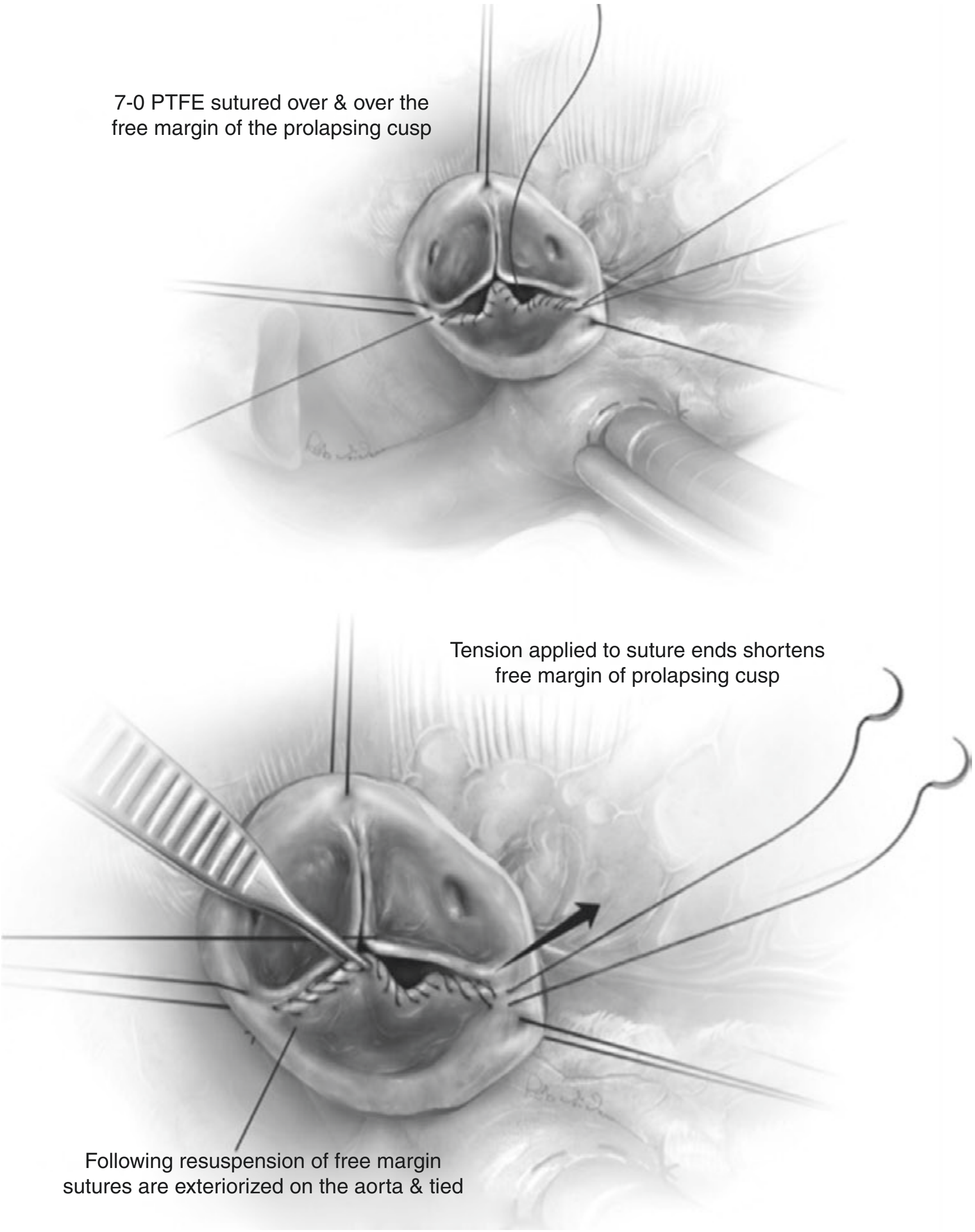

7-0 PTFE sutured over & over the free margin of the prolapsing cusp
Tension applied to suture ends shortens free margin of prolapsing cusp
Following resuspension of free margin sutures are exteriorized on the aorta & tied

Fig. 36.12 Technique of free margin resuspension using 7–0 PTFE suture. (From Boodhwani M, El Khoury G. Aortic Valve Repair. Operative Techniques in Thoracic and Cardiovascular Surgery 2009;14:266–80, with permission)

figuration with commissural angle that varies between 120° and 180°. The larger, conjoint cusp occupies a greater proportion of the valve circumference and inserts in a higher position compared to the small cusp. The large cusp has an undeveloped commissure or pseudo-commissure as well as a raphe, which marks the point of fusion. The raphe can be restricted, calcified, fibrotic or prolapsing. Sievers et al. classified bicuspid aortic valves based on the presence and number of raphes. Type 1, the most common, has frequently the fusion of the right and left coronary cusp. Type 0 bicuspid valves are symmetrical with commissure orientation at 180°, and raphe is not present. Although the mechanism of aortic insufficiency in type 0 valves are most frequently cusp prolapse, the mechanism of aortic insufficiency for type 1 bicuspid valve can often be due to restriction of the conjoint cusp at the raphe level. This leads to a triangular gap in the coaptation line.

Besides the cusp abnormalities, BAV is most frequently associated with abnormality of the functional aortic valve annulus and aortopathy. Techniques to treat cusp prolapse in BAV are similar to tricuspid aortic valve. Free margin plication or resuspension can be applied as illustrated before. The non-prolapsing cusp often serves as the reference point for restoration of the effective height of the prolapsing cusp. In case of prolapse of both cusps, the reference for height correction should be the midpoint of the aortic root. The treatment of the restricted conjoint cusp may require resection of the raphe. In case of mildly fibrotic and thickened raphe, the shaving technique can be applied (Fig. 36.13). This technique increases

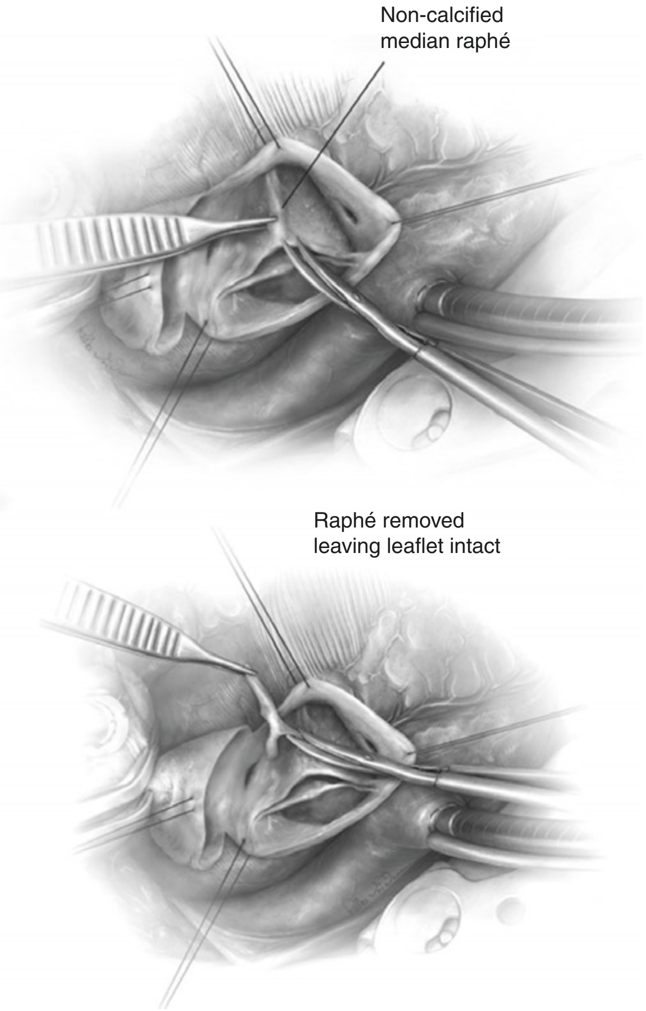


Fig. 36.13 In type 1 valves, the median raphe was addressed first. If the raphe was relatively mobile and only mildly thickened and fibrosed, it was preserved and shaved using a combination of a scalpel and scissors. (From Boodhwani M, El Khoury G. Aortic Valve Repair. Operative Techniques in Thoracic and Cardiovascular Surgery 2009;14:266–80, with permission)

the cusp mobility without the need to resect the raphe. However, in cases of severe fibrosis and calcification, parsimonious triangular resection may be required. Primary closure with 5-0 or 6-0 polypropylene in locking or interrupted fashion should be applied. If primary closure is not achievable, cusp restoration with bovine pericardial patch may be applied (Fig. 36.14). Then, the conjoint cusp effective height is compared to the other cusp. Free margin plication or resuspension may be necessary to correct any unmasked prolapse. Cusp repair has not been associated with decreased long-term outcomes in tricuspid and bicuspid aortic valves [33].

In addition to the restoration of cusp prolapse or restriction, stabilization of functional aortic annulus is critical for long-term durability in BAV repair. Bicuspid aortic valve disease is frequently associated with dilation of the aortic root and the VAJ [34]. Therefore annular stabilization techniques are a critical element of BAV repair. When aortic root replacement is indicated, re-implantation technique can provide a durable stabilization of the VAJ [34]. A lower size cut-off value (40–45 mm) for root replacement has been advocated to facilitate BAV repair especially in the presence of elevated coronary ostia, poor aortic tissue quality, and annulus size >26 mm [34]. Although re-implantation technique provides superior long-term stabilization of the aortic annulus compared to remodeling technique [35–38] and SCA [39] for BAV, some centers have shown comparable result using remodeling technique plus circumferential ring annuloplasty for stabilization of the VAJ [40, 41]. External annuloplasty seems to provide a more robust reduction of the aortic annulus (VAJ) with decreased transvalvular gradients compared to subcommissural annuloplasty [42].

Outcomes

The rationale for aortic valve repair is based on a reduction in valve-related complications compared to surgical prostheses. The low durability of bioprostheses and increased risk of bleeding and thromboembolic events with mechanical valves are the main drawbacks of surgical valves. Unfortunately, there is no randomized clinical trial comparing aortic valve repair to aortic valve replacement with either biological or mechanical valves. However, many series have shown that valve-related complications are decreased with aortic valve repair. Although contemporary surgical bioprostheses have decreased valve-related complications [43] in comparison to the older generation valves [44], aortic valve repair seems to provide better longer durability and valve-related events when indirectly compared to contemporary biological valves for young adults [1, 7, 45]. Also, aortic valve repair has a lower linearized rate of bleeding, thromboembolic events, and endocarditis [46]. Even low-dose warfarin regimen for mechanical aortic valve has shown high linearized rates of bleeding risk and thromboembolic events [47] in comparison to aortic valve repair series [1, 3]. The important outcomes after aortic valve repair include late freedom from reoperation, recurrent aortic valve insufficiency or stenosis, and the incidence of thromboembolism, bleeding and endocarditis.

Outcomes for Overall Population

Given the lack of randomized clinical trials and the heterogeneity of indications and patient populations, outcomes for aortic valve repair are frequently reported for specific subgroups of patients undergoing aortic valve repair. The indications for aortic valve repair include either aortic aneurysmal disease, aortic valve insufficiency or a combination of both. In addition to the multiple indications for aortic valve repair surgery, the different valve phenotype such as congenital, bicuspid and tricuspid aortic valves make unselected data scarce. However, a few reports for overall population have been published.

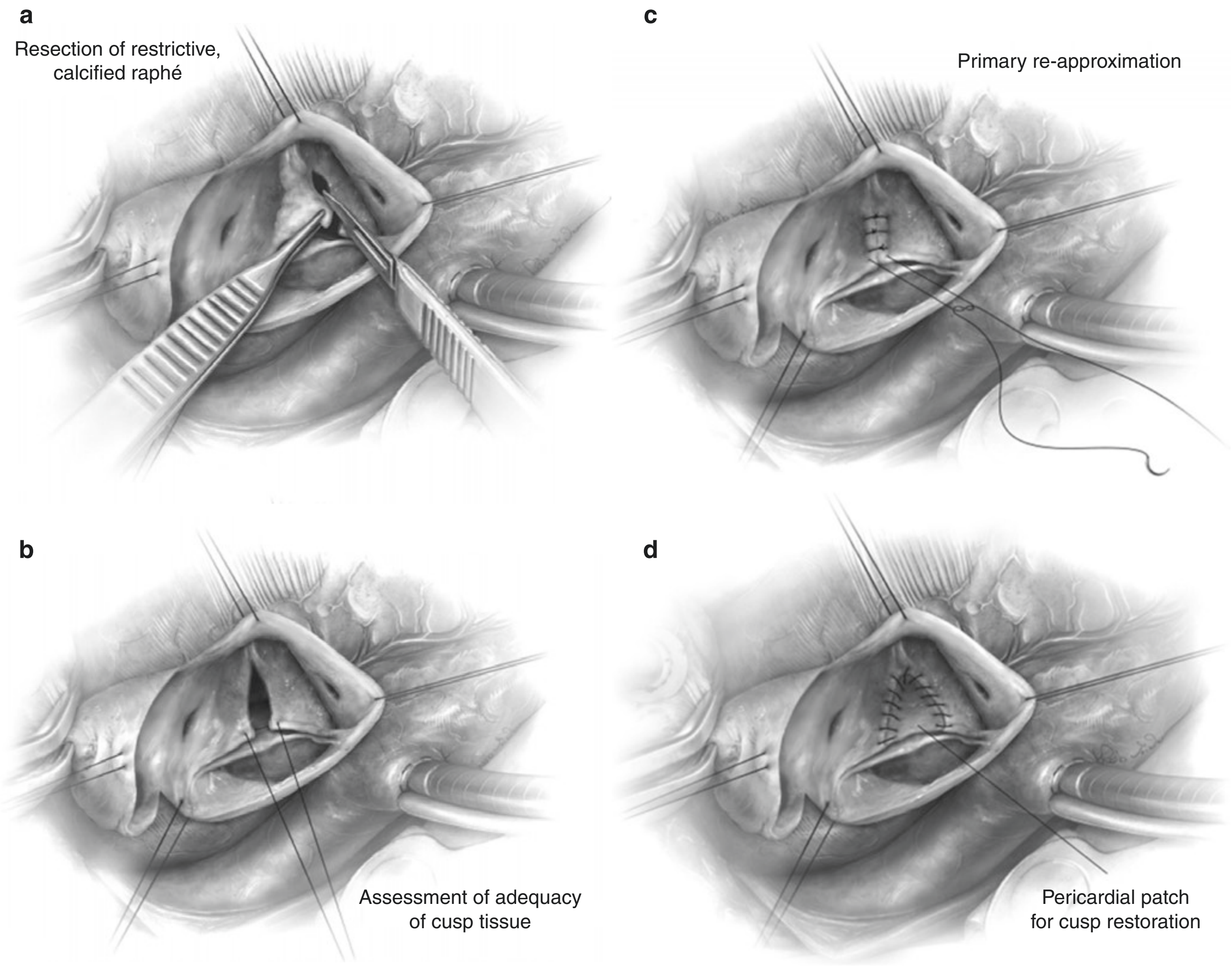

a
Resection of restrictive, calcified raphé
c
Primary re-approximation
b
Assessment of adequacy of cusp tissue
d
Pericardial patch for cusp restoration

Fig. 36.14 (**a**) Parsimonious resection of a calcified raphe. (**b**) Assessment for cusp restoration using 6-0 polypropylene. (**c**) Primary closure with 6-0 locking or interrupted sutures. (**d**) Bovine patch for cusp restoration. (From Boodhwani M, El Khoury G. Aortic Valve Repair. Operative Techniques in Thoracic and Cardiovascular Surgery 2009;14:266–80, with permission)

In a study examining the role of aortic insufficiency classification of surgical techniques and outcomes, our group evaluated 264 unselected patients undergoing aortic valve repair (mean 54 ± 16 years; 79% male). Approximately two-thirds of patients were identified as having a single lesion. Two lesions were identified in 30% and three in 6% of these patients. Also, fifty percent of lesions were type I, 35% were type II, and 15% were type III. Freedom from aortic insufficiency ≥2+ was significant higher for type III lesion compared to type I and II lesions at 5 years [6] (Fig. 36.15). El Khoury and colleagues [3] examining the effects of valve-related complications on an extension of this same cohort (475 all-comers; 81.1% male; mean age 52.9 ± 16.1, mean follow-up of 4.6 year [range 0.02–14.7]) over a longer period (15 years) found that overall survival, freedom from cardiac death, and valve-related death at 10 years were 72.8% ± 4.5%, 80.5% ± 4.2% and 89.8% ± 3.1%, respectively (Fig. 36.16). Schafers and colleagues reported their results for a series of 640 patients who had undergone repair over a 12-year period. They reported overall survival of 80% at 10 years in a population with a mean age of 56 years [1]. In a slightly smaller series of 366 patients, Svensson and colleagues reported overall survival of 74% at 10 years [48].

Schafers and colleagues reported linearized incidences of thrombo-embolism of 0.2% per patient per year, whereas El Khoury and colleagues had a higher thromboembolic rate (1.1%). Both series demonstrated similar low linearized rate of bleeding and endocarditis of 0.29%, and 0.19% per year, respectively. El Khoury also reported freedom from significant aortic insufficiency of 90.6% ± 1.7% at 5 years and 84.9% ± 2.7% at 10 years. Freedom from aortic valve reoperation of 93.8% ± 1.4% at 5 years and 86.0% 3.0% at 10 years with no difference between tricuspid and bicuspid aortic valves. In contrast, the freedom from reoperation at 5 and 10 years, in the Schafer series, was 88% and 81% in bicuspid and 97% and 93% in tricuspid aortic valves.

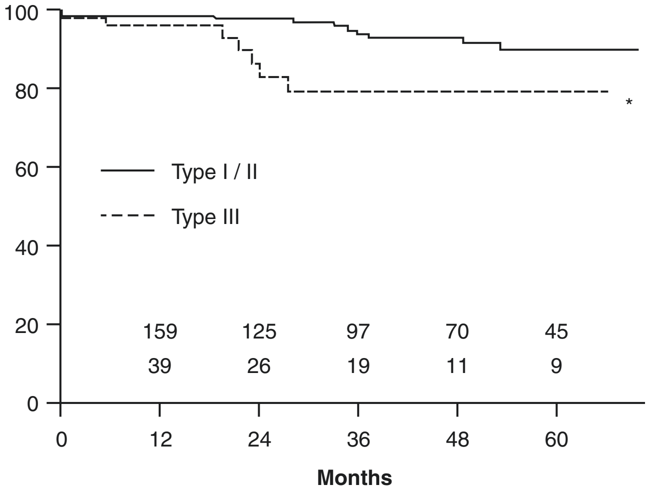


Fig. 36.15 Comparison of the recurrence of aortic insufficiency greater than 2+ between types of aortic insufficiency. Asterisk indicates P = 0.03. (Boodhwani M, de Kerchove L, Glineur D, Poncelet A, Rubay J, Astarci P, et al. Repair-oriented classification of aortic insufficiency: impact on surgical techniques and clinical outcomes. J Thorac Cardiovasc Surg 2009;137:286–94, with permission)

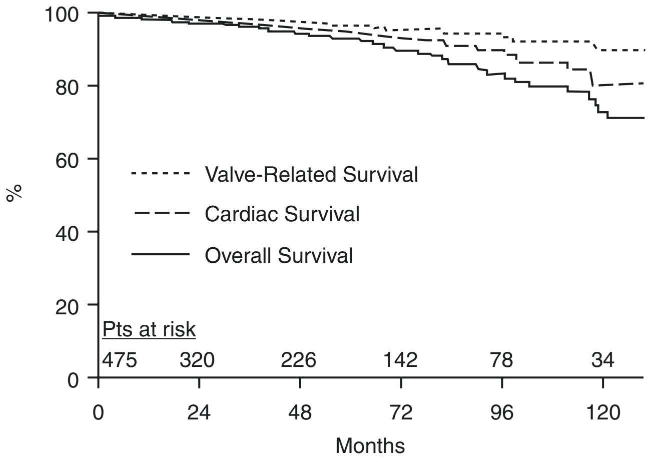


Fig. 36.16 Kaplan-Meier curves displaying overall survival (solid), cardiac survival (longer dash), and valve-related survival (shorter dash). (*pts* patients.) (From Price J, de Kerchove L, Glineur D, Vanoverschelde J-L, Noirhomme P, El Khoury G. Risk of valve-related events after aortic valve repair. Ann Thorac Surg 2013;95:606–12, with permission)

Outcomes for Aortic Valve-Sparing Root Replacement

Outcomes for aortic valve-sparing root replacement (AVRR) have been reported by multiple centres and generally show similar results. In 2015, Arabkhani and colleagues performed a meta-analysis, which reviewed the outcomes of AVRR. The mean age of operation was 51 ± 14.7 years. Reimplantation technique was used in 72% of the patients. Fourteen percent of them had BAV, and 33% had cusp repair. Early mortality was 2% and the major adverse valve-related events were only 1.66 patient-years [46]. They did not find any difference between remodeling and reimplantation techniques. Most recently, David and colleagues, the pioneers of the reimplantation technique, reported their 25 years of experience with AVRR in 371 consecutive patients with a median follow-up of 8.9 ± 5.2 years [43]. Eighty percent of the patients had reimplantation technique. Cusp repair was performed in 60.8% of the patients. Survival at 18 years was 76.8% ± 4.31%. Freedom from reoperation and aortic insufficiency greater than mild was 94.8% ± 2.0% and 78.0% ± 4.8 respectively at 18 years. Remodeling of the aortic root was marginally associated with a greater risk of reoperation on univariable analysis (HR, 3.37; 95% CI, 0.88–12.82; P = 0.07) (Fig. 36.17). Preoperative aortic insufficiency and cusp repair had no adverse effect on valve function. The authors concluded that aortic valve-sparing operations provide excellent clinical outcomes, although a slow but progressive deterioration of aortic valve function seems to occur during the first two decades of follow-up.

The same group in Toronto, using a propensity matched cohort analysis, compared AVRR to composite valve graft procedures, either bioprostheses or mechanical valves [49]. They found that AVRR was associated with reduced mortality and valve-related operations when compared to either mechanical or biological composite valve graft (Fig. 36.18).

Schafer and colleagues [50] examined their experience in 747 patients over 18 years. Hospital mortality was 2%. Overall freedom from reoperation was 92% at 10 years and 91% at 15 years. Overall freedom from reoperation was 95% for tricuspid valves at 10 and 15 years, 89% for bicuspid aortic valves at 10 years (P = 0.006), and 83% for bicuspid aortic valves at 15 years. By multivariate analysis, the strongest

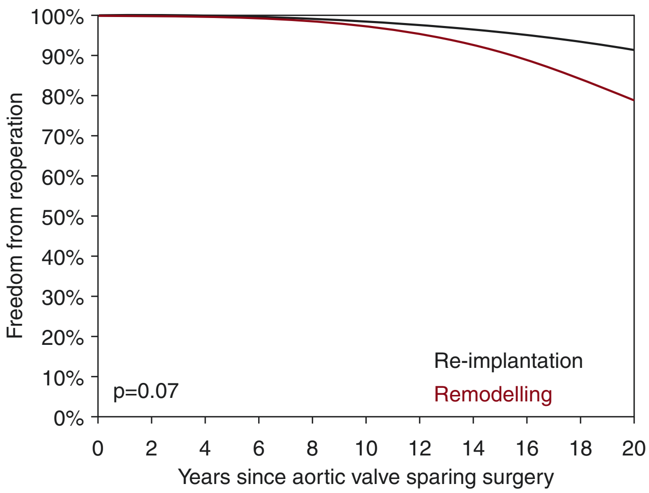
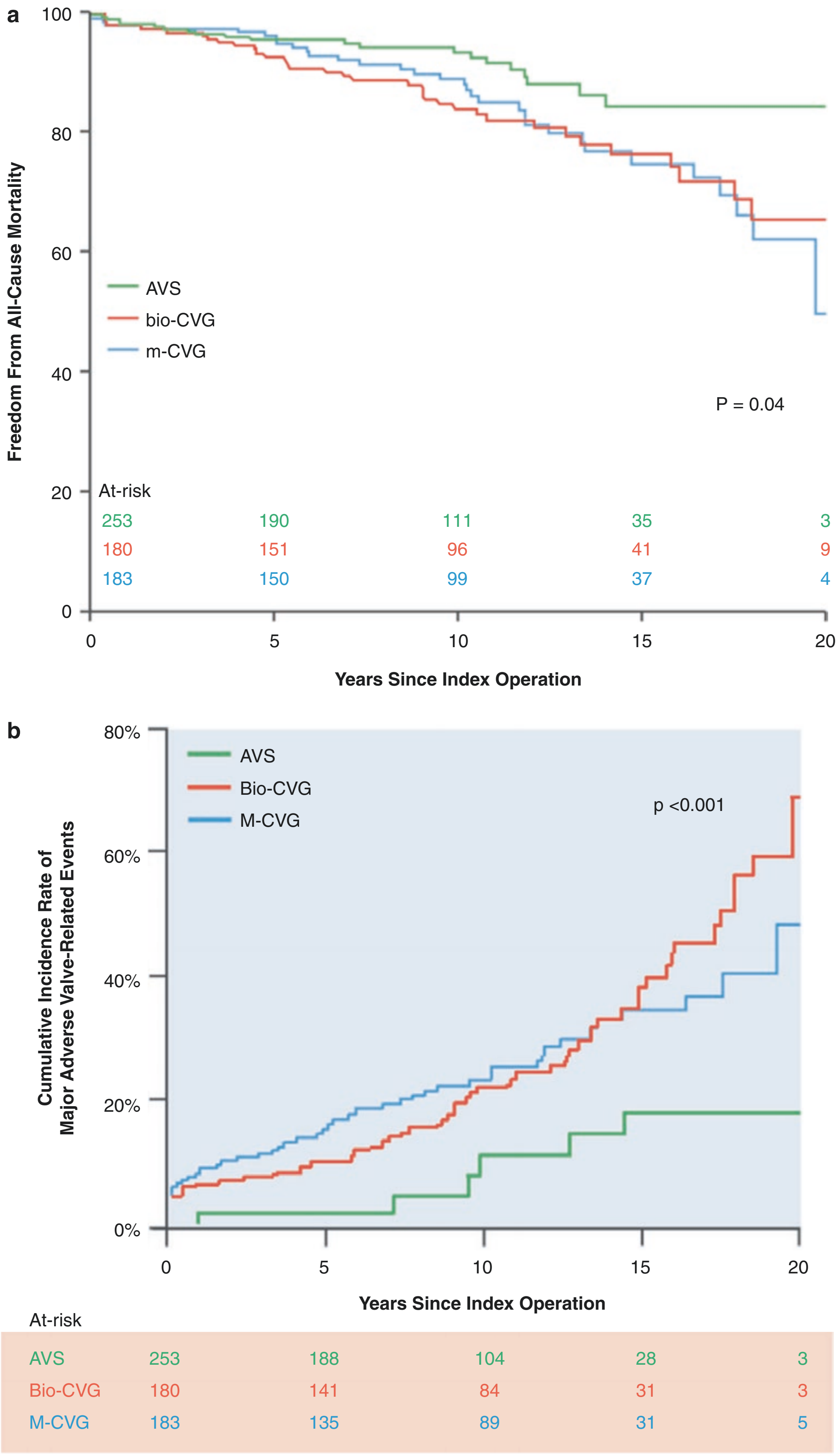


Fig. 36.17 Freedom from reoperation on the aortic valve after reimplantation and remodeling procedures. (David TE, Feindel CM, David CM, Manlhiot C. A quarter of a century of experience with aortic valve-sparing operations. J Thorac Cardiovasc Surg 2014;148:872–9, with permission)

Fig. 36.18 (**a**) All-cause mortality using Kaplan-Meier method. (**b**) Major adverse valve-related events. *AVS* aortic valve sparing, *bio-CVG* bioprosthetic composite valve graft, *m-CVH* mechanical composite valve graft. (From Ouzounian M, Rao V, Manlhiot C, et al. Valve-sparing root replacement compared with composite valve graft procedures in patients with aortic root dilation. J Am Coll Cardiol. 2016;68:1838–1847, with permission)



risk factors for failure were a VAJ of 28 mm or greater and the use of a pericardial patch as part of cusp repair. Schafers and colleagues demonstrated that the implementation of VAJ annuloplasty and systematic correction of effective height cusp of less than nine improved freedom from recurrent aortic insufficiency ≥2+.

Our group has reported outcomes of 164 consecutive patients who underwent AVRR (74% reimplantation, 26% remodeling) [51]. Severe preoperative aortic insufficiency was present in 57% of patients. In this cohort, early mortality was 0.6%, and late survival was 88% at 8 years. Freedom from reoperation was 90% at 8 years, and freedom from recurrent aortic insufficiency was 90% at 5 years with no association with preoperative aortic insufficiency severity.

Outcomes for Bicuspid Aortic Valve Repair

Outcomes for BAV repair seem to have improved in recent series as the understanding for better stabilization of aortic annulus, and the configuration of aortic valve implantation has evolved. However, differences in VAJ stabilization may be responsible for differences in the published literature. Svensson and colleagues [31] have reported their experience of BAV repair in 728 patients (mean age 42 ± 12 years, mean follow-up was 9.0 ± 6.2 years [median, 8.3]). Hospital mortality was 0.41%. Freedom from aortic valve reoperation at 10 years was 78%. Primary reasons for reoperation were cusp prolapse (38%), aortic stenosis or regurgitation (17%), and aortic regurgitation from root aneurysm (15%). Survival was 99%, 97%, 94%, 88%, and 82% at 1, 5, 10, 15, and 20 years, respectively (Fig. 36.19).

Schafers and colleagues [1] reviewing their experience of valve-related complications after aortic valve repair in 640 patients found a statistical difference in reoperation for bicuspid compared to the tricuspid aortic valve. Freedom from reoperation at 5 and 10 years was 88% and 81% in bicuspid and 97% and 93% in tricuspid aortic valves (P = 0.0013). The same group demonstrated that the implementation of suture annuloplasty to stabilize the VAJ improved repair stability [40]. El Khoury and colleagues reviewing their experience for aortic valve repair in 475 patients reported similar freedom from aortic valve reoperation in tricuspid and bicuspid valves [3]. In bicuspid patients, however, reimplantation technique reduced the risk of recurrent aortic insufficiency (P = 0.02). Similarly, David and colleagues reviewing 375 consecutive patients (bicuspid 9.2%) did not report a difference in reoperation between bicuspid and tricuspid valve reoperation and recurrent aortic insufficiency ≥2 rate. Most bicuspid patients had reimplantation technique (94.1%).

Our group has reported excellent outcomes for BAV repair. In a cohort of 122 patients (mean age 44 years; 80% male; 57% with associated aortic dilation), there was no early mortality, and late survival was 97% at 8 years. Freedom from late aortic valve reoperation was 98% and 87% at 5 and 8 years, respectively, and freedom from recurrent aortic insufficiency was 94% at 5 years. Similar to the above-mentioned studies, robust VAJ stabilization provided a more durable outcome (Fig. 36.20).

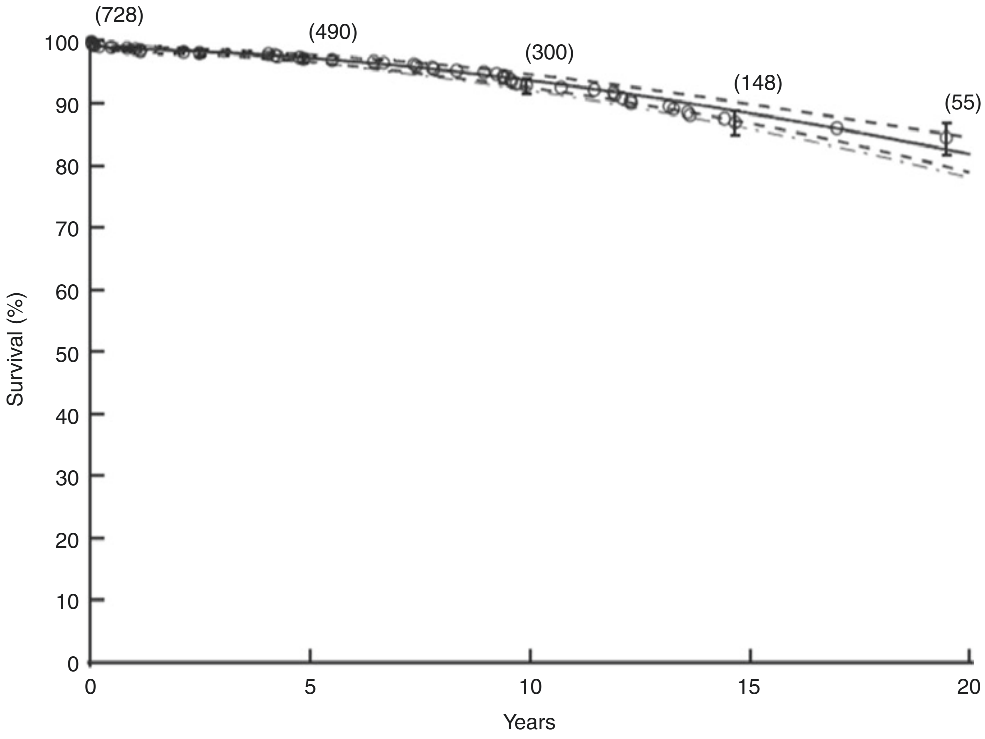


Fig. 36.19 Survival after aortic valve repair for bicuspid aortic valve disease. Each symbol (O) represents a death positioned nonparametrically, vertical bars are confidence limits equivalent to ±1 standard error, and numbers in parentheses are patients still alive. Solid line is parametric estimate enclosed within dashed 68% confidence band equivalent to ±1 standard error. Dash-dot-dash line represents survival of an age-sex-race–matched US population life table. (From Svensson LG, Al Kindi AH, Vivacqua A, Pettersson GB, Gillinov AM, Mihaljevic T, et al. Long-term durability of bicuspid aortic valve repair. Ann Thorac Surg 2014;97:1539–47, with permission)

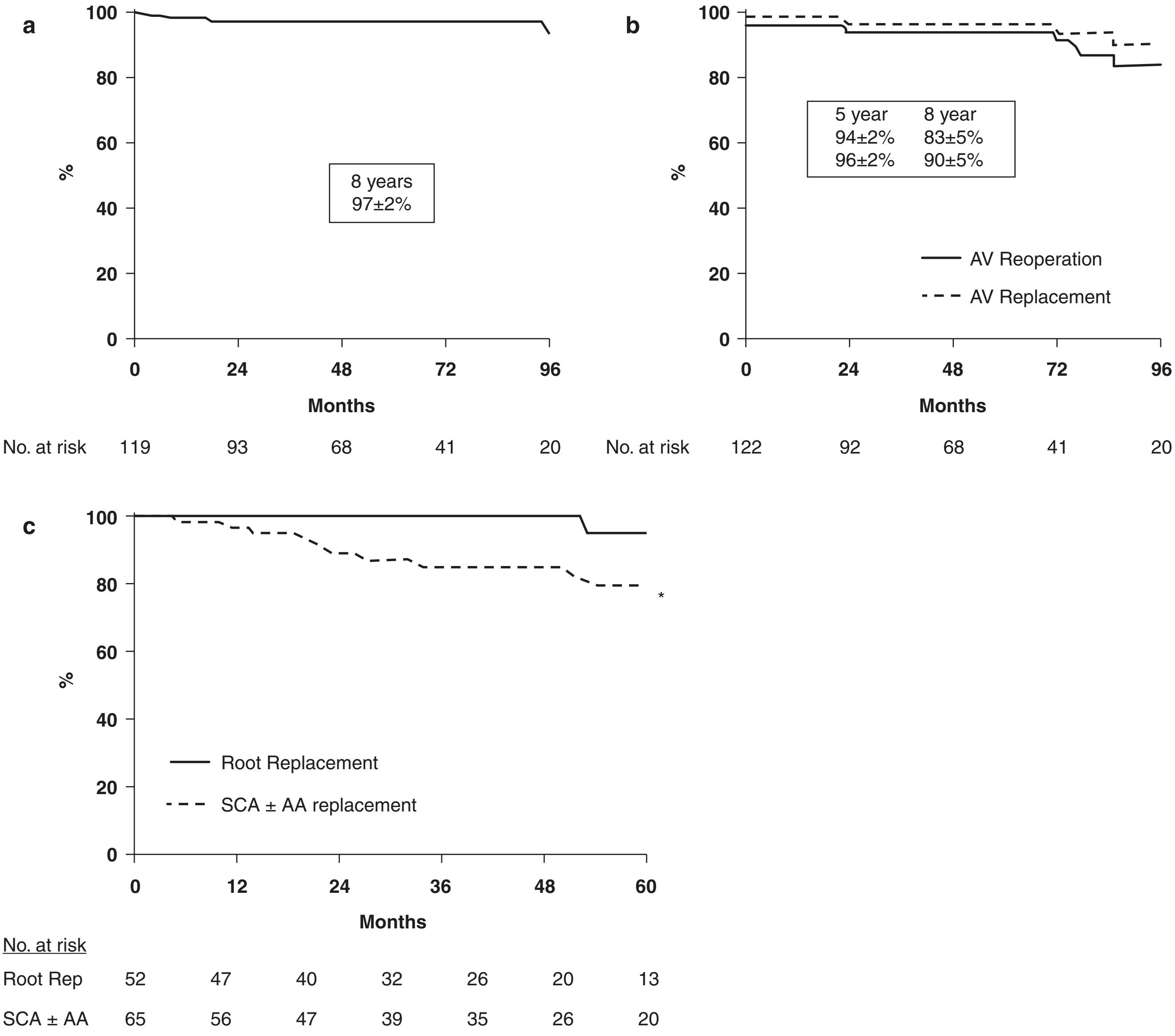


Fig. 36.20 (**a**) Overall survival was 97 ± 2% at 8 years. (**b**) Freedom from aortic valve (AV) reoperation and replacement was 94% ± 2% and 96% ± 2% at 5 years, respectively. (**c**) Patients undergoing aortic root replacement have a significantly lower recurrence of aortic insufficiency (AI) compared with those undergoing subcommissural annuloplasty (SCA) with or without ascending aortic (AA) replacement (*P = 0.03). (From de Kerchove L, Boodhwani M, Glineur D, Vandyck M, Vanoverschelde JL, Noirhomme P, et al. Valve sparing-root replacement with the reimplantation technique to increase the durability of bicuspid aortic valve repair. J Thorac Cardiovasc Surg 2011;142:1430–8, with permission)

Conclusion

Aortic valve repair has matured to become a safe, feasible and durable operation for the treatment of aortic insufficiency and aortic root aneurysms. Similar outcomes are achieved for both bicuspid and tricuspid aortic valves when repair-oriented classification and correct annular stabilization techniques are applied. Areas for improvement include a better understanding of most durable technique for annulus stabilization and cusp repair, more granular long-term data of aortic valve repair in different age groups, consistency in outcome reports among different centers, and the conduct of a randomized clinical trial comparing this technique to aortic valve replacement.

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The Small Aortic Root

37

John R. Doty

High Yield Facts

- The aortic root is considered small when the diameter of the aortic valve annulus measures 21 mm or less in adult patients.
- Implantation of a small valve can result in a condition known as patient-prosthesis mismatch.
- The diameter of the sinotubular junction is normally about 90% of the diameter of the annulus in younger patients, becoming more equal to that of the annulus in older patients.
- Replacement of the aortic valve with any mechanical valve that is 23 mm or larger according to the manufacturer's size should provide an adequate orifice that is hemodynamically suitable for most adult patients.
- The size recommendation for bioprosthetic valve replacement in the small aortic root using a stented bioprosthesis is similar to that for mechanical valves.
- Stentless valves are an attractive option for small aortic root.
- Rapid deployment sutureless valves are quite useful in the setting of small aortic root.
- Aortic homograft and pulmonary autograft are appealing options for aortic root enlargement.
- The Nunez operation, the Rittenhouse-Manougian operation, the Nicks operation, the Vouhe operation, and the Konno-Rastan aortoventriculoplasty are useful techniques for enlargement of left ventricular outflow tract.

Introduction

Although the collective experience with aortic valve replacement spans more than 50 years, there is no single valve that is clearly superior for all patients. The surgeon can select from a variety of valves, including mechanical prostheses, bioprosthetic xenografts, homografts, and autografts. Device hemodynamic performance, risk of thromboembolism and infection, need for anticoagulation, long-term durability, patient preference, and patient reliability all play a role in proper valve selection.

In patients with morphologic narrowing of the aortic root, the choice of valve has greater implications. The surgeon often is limited in the size of the replacement device, and the obstructive nature of the various valves is compounded in the small aortic root. Aortic root enlargement and replacement procedures are key components of the proper treatment of these patients, in whom operative technique directly influences long-term results.

The aortic root is considered small when the diameter of the aortic valve annulus measures 21 mm or less in adult patients. An important consideration for the surgeon is to ensure that the patient receives a prosthetic valve that is adequately sized to achieve low transvalvular gradients. Implantation of a small valve can result in a condition known as patient-prosthesis mismatch and occurs when the effective orifice area of a normally functioning prosthesis is too small in relation to the patient's body size [1]. Patient prosthesis mismatch has been associated with worse functional class, higher operative mortality, reduced survival, and more adverse cardiac events. It is imperative on the surgeon, therefore, to make the appropriate decisions regarding type of valve for implantation and the need for aortic enlargement. The techniques for enlargement or replacement of the aortic root also vary and must be tailored to the individual patient.

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Relevant Aortic Root Anatomy

The aortic valve normally has a three-cusp architecture, and the leaflets coast centrally to achieve competence. The three highest points of attachment around the annulus are termed the commissures and are situated well above the ventriculoaortic junction. The lowest point of attachment for each leaflet rests below the ventriculoaortic junction. The triangular space directly inferior to each commissure is called the interleaflet triangle, and the tissue in this area is pliable and flexible. The posterior triangle, which is located between the left and noncoronary sinuses of Valsalva, is in line directly over the midpoint of the anterior leaflet of the mitral valve. There are no chordae tendinae at this portion of the anterior leaflet of the mitral valve, allowing safe incision during posterior root enlargement.

The anterior relationships of the aortic valve also are important, particularly when removal of the pulmonary trunk for autografting is planned. The conduction system courses below the anterior commissure and the midpoint of the right coronary sinus, on the posterior rim of the membranous septum, before traveling down the ventricular septum to the right of the septal papillary muscle. Anterior incision of the aortic root to the right of the septal papillary muscle can interrupt the conduction system.

The first septal branch of the left anterior descending coronary artery runs directly below the posterior cusp of the pulmonary valve, near the medial posterior commissure. The septal branch crosses the infundibular septum to supply the septal papillary muscle. Injury to the first septal branch can result in a septal myocardial infarction and heart block from interruption of the blood supply to the bundle of His.

Aortic Root Sizing

Anatomic studies of the dimensions of the normal aortic root have determined ratios for measuring or calculating the diameter of the root at various levels. Generally, surgeons consider the aortic annulus to be at the level of the ventriculoaortic junction, which is the same diameter that is measured to determine the size of a prosthetic valve. Normal dimensions or diameter of the aortic annulus related to body size or surface area have been determined, and nomograms have been established. The diameter of the sinotubular junction is normally about 90% of the diameter of the annulus in younger patients, becoming more equal to that of the annulus in older patients [2]. The diameter of the sinotubular junction is always abnormal when it exceeds that of the aortic annulus.

Mechanical Valves

Replacement of the aortic valve with any mechanical valve that is 23 mm or larger according to the manufacturer's size should provide an adequate orifice that is hemodynamically suitable for most adult patients. Valves that are smaller than this can create flow obstruction and should probably only be used for patients with a body surface area of less than 1.5 m^2 and who are relatively sedentary. Mechanical valves smaller than 19 mm may have a prohibitive pressure gradient across the valve and caused severe outflow tract obstruction. This gradient should be considered in its relationship to the long-term resolution of left ventricular hypertrophy that results from chronic aortic stenosis.

All mechanical prosthesis that are currently designed for aortic valve replacement and available for implantation may be considered essentially equivalent. All require long-term anticoagulation and have similar performance for thromboembolic events, valve thrombosis, and anticoagulant-related hemorrhage [3, 4]. All have excellent long-term durability and by the nature of design introduce some amount of turbulent flow. The sewing ring and housing for each valve create a fixed physical obstruction, reducing the diameter of the actual orifice of the valve approximately 5–8 mm compared with the outside diameter of the device. However, the rigid nature of the mechanical valve housing prevents distortion of the annulus when securing the sutures, ensuring that there is no further narrowing of the left ventricular outflow tract (LVOT).

Bioprosthetic Valves

An ever-widening range of bioprosthetic valves is available for aortic valve replacement, and some are more useful with the patient with small aortic root. Several centers now have long-term experience with both porcine and bovine pericardial valves in the aortic position [5, 6]. Biologic prostheses are limited by durability but do not require anticoagulation. The support structure of a stented bioprosthetic valve results, however, in an approximately 5–8 mm reduction in the outflow tract. Therefore, the size recommendation for bioprosthetic valve replacement in the small aortic root using a stented bioprosthesis is similar to that for mechanical valves.

The stentless valves are an attractive option because these valves show good hemodynamic performance even in smaller sizes when placed in a subcoronary position. When same-size external stented bioprosthetic valves are compared, stentless valves have a considerably larger internal diameter. Stentless valves inserted within the intact aortic root using a free hand technique reduce the size of the outflow tract by about 2 mm, or the thickness of the aorta of the bioprosthesis. Studies comparing stentless bioprosthesis, stented prostheses, and mechanical valves have shown better regression of left ventricular hypertrophy with the stentless valves [7].

Of the major stentless bioprostheses that have been developed, only the Medtronic Freestyle valve remains in widespread use. This bioprosthesis is derived from a porcine aortic root preserved in glutaraldehyde at zero net pressure on the valve and alpha amino-oleic acid to reduce calcification of the valve. This particular device can be implanted using the subcoronary technique, the root inclusion technique, or as a freestanding aortic root replacement. For the subcoronary technique, the sinus aorta is removed from the right and left coronary sinuses of the Freestyle bioprosthesis. The preservation technique of this prosthesis aids in proper implantation because even the trimmed graft holds its shape well, and the patient's native aorta may be conformed to the graft aorta in a reproducible fashion.

Full root replacement with the Freestyle bioprosthesis is particularly applicable to patients with a small aortic root. The aorta is divided above the sinotubular junction and both coronary ostia are mobilized on generous buttons of aortic sinus tissue. The remaining sinus aorta is removed, the aortic valve is excised, and the annulus is debrided. A larger prosthesis may now be employed because the device stands by itself on top of the aortic root and is not enclosed within the aorta. The bioprosthesis is implanted as a complete freestanding aortic root using continuous monofilament sutures or multiple interrupted braided sutures to attach the inflow sewing cuff to the aortic annulus. The coronary buttons are implanted in the appropriate position, and an end-to-end anastomosis of the distal end of the graft is constructed to the ascending aorta. Abnormally dilated or aneurysmal ascending aorta may be resected and replaced with a synthetic graft.

The root inclusion technique is not recommended for implantation of a stentless prosthesis in patients with a small aortic root. These devices are relatively stiff and are subject to distortion when the aorta is closed over them. In addition, the hemodynamic advantages of aortic valve replacement by aortic root techniques are lost when the device is within the aorta of the patient.

Rapid-deployment "sutureless" valves are newer bioprosthetic valves that are mounted on a balloon expandable stent system which replaces the traditional sewing ring. After resection of the aortic valve leaflets and debridement of the annulus, a few guiding sutures are placed at the level of the aortic annulus. The annulus is measured, and an appropriately sized prosthesis is selected. These valves are inserted in a constrained form and positioned at the level of the aortic annulus. An internal balloon system is used to expand the supporting cuff of the valve and secure it in the LVOT by outward radial force. These valves are quite useful in the small aortic root, as the stent expands and enlarges the annulus in a circular form, rather than possibly narrowing the LVOT when tying sutures with a traditional stented bioprosthesis [8].

Aortic Homograft

As with stentless bioprostheses, aortic homografts are versatile, flexible tissue that has excellent hemodynamic performance in the aortic position. The homograft can be preserved with various techniques; the cryopreservation method appears best. Homografts are particularly well suited for use in the small aortic annulus, often without root enlargement, and can be used to enlarge the root when necessary. These valves do not require anticoagulation and are resistant to thromboembolism and endocarditis.

Originally, aortic homografts were implanted in a subcoronary position after removal of all aortic sinus tissue. Modification of this technique by retaining the noncoronary sinus, as described by Ross, ensures more reliable valve implantation by fixing the position of two of the three commissures. The entire aortic root can also be replaced using a freestanding root technique. Mini root or cylinder inclusion techniques are a less desirable approach for homograft implantation. If the patient requires only valve replacement and has a normal aorta, the non-coronary sinus technique allows for the smallest amount of homograft tissue to be implanted.

Root enlargement with aortic homograft is a useful technique that can be tailored to the severity of outflow tract obstruction. The posterior interleaflet triangle can be incised and a portion of the noncoronary sinus removed for isolated annular stenosis. In patients with subvalvular obstruction, the incision is carried down onto the midportion of the anterior leaflet of the mitral valve. The attached homograft mitral valve is used to repair the defect in the recipient's mitral valve, and the homograft noncoronary sinus is used to close the aorta after valve implantation.

Experience with the cryopreserved aortic homograft has shown excellent freedom from thromboembolism and endocarditis in long-term analysis [9, 10]. Death from valve related causes is infrequent, and the homograft has reasonable long-term durability. The noncoronary sinus technique or its variant with root enlargement is superior to other methods in offering the best chance for freedom from valve explantation. Late degeneration of the valve is probably related to a combination of technical and immunologic factors.

Pulmonary Autograft

The pulmonary autograft operation, or Ross procedure, offers a few distinct advantages for aortic valve replacement. It is particularly applicable to patients with the small aortic root because the native pulmonary annulus is normally about 2 mm larger than the native aortic annulus, and pulmonary autografting results in a small valve upsize. Long-term performance of the pulmonary valve in the aortic position depends on development of annular or autograft root dilation [11, 12]. Because the autograft is the patient's own tissue, the accelerated calcification and degeneration seen with other bioprosthetic valves is unlikely. Patients do not require anticoagulation, and studies using this procedure in the setting of endocarditis highlight the autograft's inherent resistance to infection.

In the operation, the aortic valve and root are excised, retaining only the fibrous aortic annulus and the coronary ostia with sinus aortic buttons. The patient's own pulmonary trunk is excised, including the pulmonary valve. The pulmonary trunk is attached to the fibrous annulus of the aortic root using interrupted stitches. A strip of pericardium or felt is incorporated by tying the sutures around this strip. This is known as the supported root technique and helps prevent late annular dilation and valve incompetence by fixing the size of the outflow tract at the level of the pulmonary valve. The coronary arteries are implanted, and the distal end of the pulmonary trunk is attached to the ascending aorta. The diameter of the sinotubular junction is also fixed by prosthetic material to prevent dilation. The right ventricular outflow tract is reconstructed with a homograft pulmonary trunk. The use of a devascularized pulmonary homograft may achieve better immunologic tolerance.

Root enlargement techniques may be combined with the pulmonary autograft operation. The left ventricular outflow tract should be altered to match the size of the native pulmonary trunk. Attempting to place a large pulmonary trunk into the small aortic root may cause distortion or stenosis of the pulmonary valve, as would deliberate narrowing of the autograft before implantation, and ultimately would result in valve failure. Similarly, an enlarged aortic root should be reduced to appropriate anatomic dimensions to match the native pulmonary trunk.

After removal of the pulmonary trunk, the ventricular septum can be incised to widen the LVOT, known as the Ross–Konno operation. This incision is not as deep as the classic Konno operation and prevents injury to the first septal branch. More complete relief of outflow tract obstruction can be achieved by progressive shaving of myocardium from the left side of the septum. The pulmonary autograft is seated deeply in the outflow tract by attaching it to the ventricular septum, and any septal defect may be filled with attached myocardium on the autograft. This approach allows precise matching of the diameter of the outflow tract to the diameter of the autograft.

The pulmonary autograft operation has a few disadvantages. It is more complex than isolated valve replacement and carries a higher operative mortality, and is therefore best applied to selected younger, athletic patients who will benefit from the superior hemodynamic performance. The aortic valve disease is resolved by using autologous tissue, but the pulmonary root tissue may be susceptible to later dilation. In addition, the pulmonary homograft in the right ventricular outflow tract is susceptible to degeneration and will eventually require reintervention.

Operations for Aortic Root Enlargement

In addition to enlargement of the aortic root by aortic homograft or pulmonary autograft, there are several techniques that can be employed for enlargement of the LVOT. These include the Nunez operation, the Rittenhouse-Manougian operation, the Nicks operation, the Vouhe operation, and the Konno-Rastan aortoventriculoplasty. A variant of aortoventriculoplasty, the Ross-Konno operation, already has been described. Most enlargement procedures in adult patients are best performed via a posterior aortic root approach.

The Nunez technique enlarges the aortic root posteriorly by extending the aortotomy incision through the posterior commissure into the underlying interleaflet triangle. This incision allows separation of the complaint tissues in the interleaflet triangle enlarges the LOVT by 2–3 mm. A prosthetic patch is placed in the posterior commissure, and a larger prosthetic valve can be inserted. The prosthetic patch is tapered to close the non-coronary sinus and aortotomy. Additional enlargement of the aortic root can be obtained with the Rittenhouse-Manougian operation, which further extends this incision into the midportion of the anterior leaflet of the mitral valve. Enlargement of 4–5 mm can be achieved in this manner, and the defect in the anterior leaflet is repaired with a prosthetic patch. The patch repair is continued across the defect in the roof of the left atrium. A larger prosthetic valve is inserted, and the noncoronary sinus and aortotomy are reconstructed in a similar fashion.

The Nicks technique also creates posterior enlargement by extending the aortotomy into the noncoronary sinus. The left atrium is opened laterally to the aortic incision, and the aortotomy incision is extended into the anterior leaflet of the mitral valve. This incision is slightly off center in the anterior leaflet and must be shifted to the exact midportion of the leaflet. A prosthetic patch is used to reconstruct the defect in the anterior leaflet of the mitral valve and the left atrium, and a larger prosthetic valve is inserted. Enlargement of 2–5 mm can be obtained by this operation.

The Vouhe and Konno-Rastan techniques are anterior enlargement methods primarily used in children. In the Vouhe operation, an incision is made in the commissure between the left and right coronary cusps and extended down through the interleaflet triangle through the aortic annulus. The Konno-Rastan aortoventriculoplasty for anterior enlargement of the LVOT is used when extensive enlargement is required of more than 4–5 mm in diameter. It is traditionally used in small children for placement of a large prosthesis that can accommodate growth, but it is also useful in patients with subaortic tunnel stenosis. A vertical incision is made in the aorta into the right coronary sinus and extended into the right ventricular outflow that anteriorly. The ventricular septum is incised at the aortic annulus, extending to the left of the conduction system. The first septal branch is at risk of injury during this part of the procedure. The annulus of the aortic valve is widened greatly, and the valve cusps are removed. A diamond shaped patch is used to repair the defect in the ventricular septum to the level of the annulus, a large prosthetic valve is inserted, and the patch repair is continued to close the aortotomy. A second patch is used to repair the right ventricular outflow tract.

Conclusion

The surgeon must be prepared to use a range of valve replacement devices in combination with aortic root enlargement techniques for patients with a small aortic root. Regardless of the choice for valve replacement, all currently available valves carry an inherent risk for late failure and need for replacement. Mechanical prostheses may thrombose, become infected, or suffer excessive pannus formation. Bioprosthetic and homograft tissue degenerate and calcify over time, rendering the valves stenotic, incompetent, or both. The pulmonary autograft may become aneurysmal and produce autograft valve insufficiency, and the associated pulmonary homograft eventually degenerates. Aortic valve re-replacement is generally associated with increased operative risk and represents a unique surgical challenge when required in the patient with a small aortic root.

Current recommendations for choice of valve prosthetic selection in this patient population are based primarily on patient age and activity. For children and young adults, the pulmonary autograft operation with root enlargement or reduction as necessary to match the LVOT is suitable. Mechanical prostheses are acceptable for nearly any patient age except the elderly, and the root should be enlarged to accommodate at least a 23 mm prosthesis. In patients older than age 50, a stentless bioprosthetic valve may have the best hemodynamic performance, particularly in the smaller sizes. When a stented bioprosthesis is used, the root should be enlarged to implant a 23 mm or larger valve. If adequate root enlargement is not attainable through a posterior approach, full root replacement or use of a rapid-deployment valve should be considered. Aortic homografts are limited in size and are best reserved for patients with active infection or younger patients where the autograft operation is not appropriate.

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The Ross Procedure

38

Ismail Bouhout and Ismail El-Hamamsy

High Yield Facts

- The Ross procedure is the only operation that ensures long-term viability of the aortic valve substitute.
- In non-elderly adults, this translates into significant improvements in long-term clinically relevant outcomes compared to conventional aortic valve replacement, namely survival, quality of life and risk of valve-related complications.
- The Ross procedure results in restored survival in non-elderly adults when compared to a sex- and age-matched general population.
- Long-term studies report an annualized risk of reintervention on the autograft of ~1% patient-year and 0.5% patient-year for the pulmonary homograft.
- The rate of reintervention is twofold higher in patients with aortic regurgitation and a dilated aortic annulus when compared to those operated for aortic stenosis.
- Aortic root expertise and surgical technique have a direct impact on long-term stability of the pulmonary autograft after the Ross procedure.

Introduction

The Ross procedure consists of replacing the diseased aortic valve with the patient's own pulmonary valve and represents the only replacement operation that ensures long-term viability of the aortic valve substitute. The right ventricle outflow tract is then replaced with a pulmonary homograft (or in some cases a xenograft). Having a living aortic valve and root in the Ross procedure translates into several potential benefits compared to conventional aortic valve replacement (AVR), particularly in young and active patients such as late survival approaching that of the matched general population, excellent quality of life and hemodynamics and a low rate of valve-related complications [1–5].

Historical Perspective

Donald Ross first described the Ross procedure in 1967 [6]. The original description involved a subcoronary implantation technique, which avoided the need for coronary reimplantation. Since then, many surgical modifications have been adopted with the full root replacement being the most widely adopted technique [3], although the subcoronary or inclusion techniques are still performed by some groups with excellent results [7]. Followed by a wave of enthusiasm in the 1990s, the Ross procedure has been largely abandoned in adults, representing <1% of all AVRs performed in North America, according to a 2014 STS database analysis [8]. This is in part due to concerns with technical complexity of the operation and long-term durability of the pulmonary autograft [9]. In the last decade, there has been a global renaissance for the operation, which resulted from publication of several studies reporting long-term results following the Ross procedure.

Rationale

The aortic valve and root is a highly sophisticated structure that performs many complex functions, all of which allow a normal tri-leaflet valve to open and close >100,000 times/day with a perfect laminar flow [10–15]. Therefore, the rationale for the Ross procedure is that a living substitute would result in improved outcomes because of its better hemodynamics, its growth capacity in children, its low thromboembolic risk, the absence of required anticoagulation and its resistance to infection.

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Table 38.1 A summary of comparative outcomes of valve-related complications in non-elderly adults undergoing the Ross procedure and aortic valve replacement with tissue or mechanical valve

	Ross procedure	Stented tissue valves	Mechanical prosthesis
Survival	Survival equivalent to a sex- and gender-matched general population up to 10 years after surgery	Under expected survival	Under expected survival
Valve related complications	0.4% patient-year	0.5–1% patient-year	1% patient-year
Aortic valve reintervention	1% patient-year for AS 2% patient-year for AR	1–2% patient-year	0.5% patient-year
Quality of life	Restored quality of life	Uncertain	Lower quality of life when compared to the Ross
Pregnancy	Low risk of fetal and maternal complications	Low risk of fetal and maternal complications	Significant risk of fetal and maternal complications
Hemodynamic performance	Closest profile to native aortic valve	The lowest aortic orifice area Up to 30% of PPM	Suboptimal hemodynamics 20–30% of PPM
Reproducibility	Expertise needed	Reproducible	Reproducible

AS aortic stenosis, *AR* aortic regurgitation, *PPM* prosthesis-patient mismatch

The ideal aortic valve substitute for non-elderly adults remains elusive. Traditionally, the choice of valve substitute was guided by the risk of anticoagulation against the risk of valve degeneration (Table 38.1). In fact, although mechanical prostheses are durable, they require anticoagulation and therefore expose the patient to a constant and lifelong risk of bleeding and thromboembolic events (1–2% patient year) [16]. In contrast, tissue valves are associated with an inherent risk of valve degeneration and reoperation, the latter being higher in younger patients [17]. Indeed, various studies have examined the incidence of valve-related events following AVR with biological and mechanical valves, especially in young adults, showing an incidence ranging from 30% to 50% at 10–20 years [18–22].

In recent years, there has been a paradigm shift from the traditional reoperation versus anticoagulation conundrum towards evaluating long-term survival and quality of life following various AVR procedures. This is all the more important in non-elderly patients (<60 years old) with a longer anticipated life expectancy than their elderly counterparts. Several recent studies on long-term results following biological or mechanical AVR consistently report 10- and 15-survival, ranging from 70% to 85%, significantly lower compared to the age and gender-matched general population [16, 17, 23–26]. In addition, quality of life in patients undergoing mechanical AVR was significantly impacted, mainly by the need for anticoagulation, the fear of bleeding and the sound of the prosthesis [27, 28].

Results Following the Ross Procedure

Survival

In contrast to prosthetic AVR, the Ross procedure provides a living valve substitute in the aortic position. Over the last decade, several studies have been published, examining long-term survival and valve-related complications after the Ross procedure with consistent outcomes (Table 38.2) [29]. In summary, with mean follow-up into the second decade in the majority of these studies, the Ross procedure results in restored survival in non-elderly adults when compared to a sex- and age-matched general population [1–5, 30–36]. Two recent studies have compared the Ross procedure to conventional AVR [4, 5]. After adjusting for confounding variables, these two studies have shown better survival and lower valve-related complications with the Ross procedure. Similarly, two recent meta-analyses have reported a survival advantage and a decreased rate of valve-related complications after the Ross procedure [37, 38].

Hemodynamics

The autograft is a stentless living aortic valve substitute and aortic root dynamics are preserved following the operation. Tans-valvular gradients across the pulmonary autograft are systematically <10 mmHg after surgery. Importantly, these gradients do not increase with time as observed with biological prostheses or aortic homografts, because the autograft does not calcify or degenerate [1, 33, 39]. As a result, hemodynamic performance of the pulmonary autograft valve closely matches native aortic valve function at rest and exercise [40, 41]. Similarly, using 4-dimensional magnetic resonance imaging to compare the flow pattern across the aortic root between different surgical techniques, the Ross procedure was the only operation with a flow pattern almost identical to a normal aortic root [40]. It is thought that this better hemodynamic profile exposes the left ventricle to lower strain chronically, resulting in less myocardial fibrosis, which may explain the observed difference in survival between the Ross procedure and conventional AVR.

Table 38.2 Recent reports examining long-term outcomes following the Ross procedure in non-elderly adults

Study	Population	Mean FU (years)	Mean age (years)	MR (pt-yr)	TE (pt-yr)	Major bleeding (pt-yr)	Reintervention (pt-yr)	Endocarditis (pt-yr)	Comments
Martin et al. [36] Retrospective study	310 Ross procedures	15.1	41	0.7%	–	–	AV: 0.8% PV: 0.5%	0.08%	Survival equivalent to a sex- and gender-matched general population up to 15 years after surgery.
Mazine et al. [5] Propensity-Matched Cohort study	416 patients (208 MPs & 208 Ross patients)	14.2	37	–	Ross: 0.2% MP: 0.7% (p = 0.03)	Ross: 0% MP: 0.7% (p < 0.001)	Ross: 0.6% MP: 0.3% (p = 0.18)	Ross: 0.3% MP: 0.4% (p = 0.80)	Freedom from cardiac death higher in the Ross group (97% versus 93% at 15 years)
Karaskov et al. [30] Retrospective study	741 Ross procedures	5.8	47	1%	0.23%	0.09%	AV: 0.6% PV: 1.7%	0.81%	Survival equivalent to a sex- and gender-matched general population
Miskovic et al. [34] Prospective study	209 Ross procedures	7.9	43	0.9%	0.5%	0%	AV: 0.7% PV: 0.6%	0.2%	Survival equivalent to a sex- and gender-matched general population
Mastrobuoni et al. [32] Prospective study	306 Ross procedures	10.6	42	0.7%	0.7%	–	2.1%	0.1%	Survival equivalent to a sex- and gender-matched general population up to 10 years after surgery. Curves start to diverge 10 years after procedure (at 15 year, HR = 0.93, CI 0.71–0.97).
Sievers et al. [35] Prospective study	*1779 Ross procedures*	8.3	44.7	0.3%	–	–	AV: 0.5% PV: 0.7%	–	Survival equivalent to a sex- and gender-matched general population up to 10 years.
David et al. [2] Prospective study	212 Ross procedures	13.8	34	0.3%	0.2%	–	AV: 0.9% PV: 0.4%	0.2%	Survival equivalent to a sex- and gender-matched general population.
Charitos et al. [33] Prospective study	203 Ross procedures	12.3	47	0.9%	0.4%	0.2%	1.0% (AV: 0.6% & PV: 0.5%)	0.6%	Survival equivalent to a sex- and gender-matched general population.

(continued)

Table 38.2 (continued)

Study	Population	Mean FU (years)	Mean age (years)	MR (pt-yr)	TE (pt-yr)	Major bleeding (pt-yr)	Reintervention (pt-yr)	Endocarditis (pt-yr)	Comments
Mokhles et al. [57] Propensity-Matched Cohort Study	406 patients (253 MPs & 253 Ross patients).	5.1	48	Ross: 0.7% MP: 0.4% [p = NS]	Ross: 0.4% MP: 0.1% [p = 0.10]	Ross: 0.2% MP: 0.4% [p = 0.15]	Ross: 0.6% MP: 0.0% [p = 0.01]	Ross: 0.2% MP: 0.0% [p = 0.16]	Survival of Ross and mechanical AVR patients equivalent to a sex- and age-matched population.
El-Hamamsy et al. [1] Randomized study	216 patients [108 Ross procedure & 108 homografts]	10.2	39	Ross: 0.4% Homograft: 1.7% [p = 0.02]	–	–	Ross: 0.5% Homograft: 1.8% [p = 0.0003]	Ross: 0.2% Homograft: 0.6% [p = 0.02]	Survival in the Ross group was equivalent to a sex- and gender-matched general population.

AV aortic valve, *AVR* aortic valve replacement, *BP* bioprosthesis, *CI* confidence interval, *FU* follow-up, *HR* hazard ratio, *MP* mechanical prosthesis, *MR* mortality rate, *NS* not significant, *TE* thromboembolism, *PV* pulmonary valve

Valve-Related Complications

The living nature of the autograft with normal endothelial cell lining on the neo-aortic valve translates into low thrombogenicity (endothelial cells produce nitric oxide and limit platelet aggregation) and resistance to infections. The Ross procedure has demonstrated lower risk of thromboembolic events, major bleeding and endocarditis than biological and mechanical prostheses valves, as well as aortic homografts [1, 42]. Nevertheless, regular echocardiographic surveillance of patients and lifelong endocarditis prophylaxis is recommended, especially to reduce the risk of right-sided endocarditis [43].

Reoperation

One of the limitations of the Ross procedure is the risk of reintervention, which may be required either because of autograft dilation and/or pulmonary homograft dysfunction. In some series, the rate of reoperation due to pulmonary autograft dilatation was alarmingly high, prompting some groups to abandon the operation altogether. Interestingly, in these patients with late autograft reoperation, it has been shown that most of the dilatation is already observed at hospital discharge, underscoring the importance of surgical technique on long-term success of this procedure.

In contrast, most long-term studies report an annualized risk of reintervention on the autograft of ~1% patient-year and 0.5% patient-year for the pulmonary homograft [1–5, 30–36, 44–46] . Interestingly, the two studies comparing the Ross procedure to conventional AVR found no difference in the rate of late reintervention [4, 5].

Nevertheless, patients presenting with aortic regurgitation and a dilated aortic annulus who undergo a Ross procedure, present a higher risk of late autograft reintervention. Indeed, the rate of reintervention is two-fold higher in this subgroup of patients when compared to those operated for aortic stenosis [31, 44–46]. Thought this observed difference may be due to inherent differences in pulmonary autograft biological and biomechanical proprieties, technical and patient-related modifiable factors could make a major contribution to the reintervention risk in aortic regurgitation patients, as detailed below.

Technical Considerations

Unlike standard mechanical or biological AVR, the Ross procedure is an operation which can be performed with many technical variations. These modifications have evolved through improved understanding of aortic and pulmonary root anatomical differences and careful examination of failure modes. These modifications have had a direct impact on improving long-term outcomes following the Ross procedure over time.

Although embryologically, the aortic and pulmonary roots originate from the migration of neural crest cells, and macroscopically, the pulmonary valve looks identical to a normal tri-leaflet aortic valve, there are some important distinguishing features. The aortic annulus is an anatomically distinct landmark, which sits within the fibrous skeleton of the heart, providing the aortic valve with structural support. In contrast, the pulmonary valve is not supported by an annulus per se. Rather, the pulmonary leaflets attach to infundibular muscle, which attaches to the base of the pulmonary artery. This is particularly relevant because when harvesting the pulmonary autograft, this sub-valvular infundibular muscle becomes devascularized and necrotic, and therefore cannot provide structural support to the PV and root. Another important feature of pulmonary roots is that the pulmonary vascular wall is significantly thinner than the aortic wall with fewer elastic lamellae in large part because it is exposed to lower mechanical stresses due to the lower pulmonary artery pressures. Finally, although some studies suggest that the pulmonary wall in patients with bicuspid aortic valves demonstrates signs of structural and functional anomalies similar to those observed on the aortic side (increased matrix metalloproteinase expression, smooth muscle cell breakdown and disarray, decreased fibrillin levels) [47, 48], this has not had any impact on long-term clinical durability of the pulmonary autograft in the aortic position, or on the incidence of pulmonary autograft dilatation [49, 50]. Therefore, it does not appear that the changes observed on the aortic side are present on the pulmonary side, suggesting that in a majority of patients, these wall abnormalities are more a result of hemodynamic factors, rather than genetic predetermination [51].

Nevertheless, to ensure long-term durability of the pulmonary autograft, it is important to follow some principles that are listed below (Fig. 38.1):

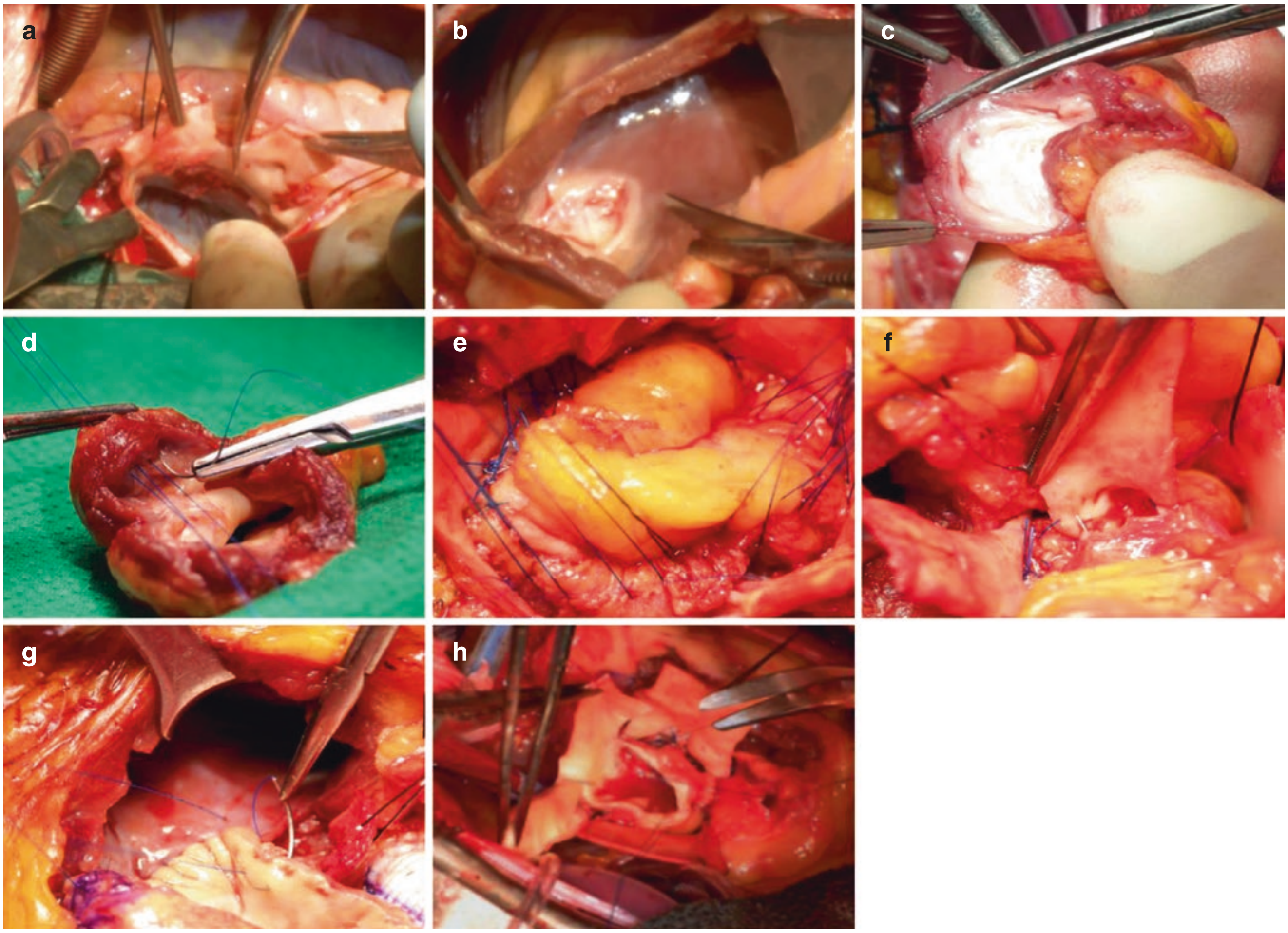

Fig. 38.1 The main operative steps of the full root Ross procedure. (**a**) Aortic valve excision and coronary mobilization. Careful attention to commissural symmetry is a key part of the operation. (**b**) Autograft harvesting, staying ~3–5 mm from the leaflet insertion line. (**c**) Pulmonary autograft preparation and infundibular muscle trimming, leaving <2–3 mm of muscle below the insertion of leaflets. In addition, the muscle is scalloped to follow the crown shape of the annulus. (**d**) Interrupted sutures placed tangentially through the pulmonary autograft wall to ensure infra-annular positioning of the autograft within the left ventricular outflow tract (LVOT). (**e**) Autograft implantation is completed by parachuting it into the LVOT and tying the sutures. (**f**) Coronary button reimplantation within their respective sinuses. Except in cases of coronary anomalies, the buttons are made within the body of the sinus, below the commissures. (**g**) Right ventricular outflow tract (RVOT) reconstruction with a cryopreserved decellularized pulmonary homograft. Alternatively, a stentless xenograft can be used for RVOT reconstruction. (**h**) Distal pulmonary autograft trimming, leaving <2–3 mm of native pulmonary artery tissue above the commissures. If the native ascending aorta measures ≥38 mm, a short Dacron tube (26–28 mm in diameter) is used as an interposition graft between the autograft and aorta, in order to prevent sinotubular junction dilatation

1. The pulmonary infundibular muscle should be trimmed during autograft harvesting to leave no more than 2–3 mm below cusp insertion. Leaving more infundibular muscle results in a supra-annular positioning of the autograft root, which results in an increased risk of autograft dilatation and aortic regurgitation.
2. In addition, the autograft should be placed in an intra-annular position (within the left ventricular outflow tract) so that the native aortic annulus supports the neo-aortic valve.
3. In patients with an annulus diameter ≥27 mm, an extra-aortic annuloplasty should be performed using a Dacron ring in order to match the pulmonary autograft to the native aortic annulus and prevent future annular enlargement. The use of annulus reinforcement in patients with a dilated annulus provides excellent stability, all the while preserving aortic annular dynamics [52, 53].
4. After autograft implantation, all supra-commissural pulmonary artery tissue should be removed, leaving ~2–3 mm above the sinotubular junction. This limits the amount of pulmonary artery tissue exposed to systematic pressures, and thus reduces the risk of dilatation at the sinotubular junction and secondary aortic regurgitation.
5. Late dilatation of the native ascending aorta can result in dilatation of the autograft at the level of the STJ, resulting in aortic regurgitation [54]. Therefore, the ascending aorta should be replaced by a short interposition Dacron graft in patients when the ascending aortic is >38–40 mm. Alternatively, an annuloplasty ring can be used to stabilize the STJ and prevent late dilatation.
6. Biomechanical studies have shown that physiological adaptation of the autograft to systemic conditions is possible when the wall stress applied to the pulmonary autograft is in the lower range of the strain-stress curve [55, 56]. This occurs through thickening of the pulmonary wall mediated by increased collagen deposition. Therefore, it is imperative to control the blood pressure during the early autograft adaptive period (6–12 months) using beta blockers as first-line therapy to decrease dp/dt.
7. Although pulmonary homograft supravalvular stenosis is infrequent, its occurrence follows a bimodal presentation. The early hazard phase occurs in the first 12–18 months, which is thought to be the result of an inflammatory process in the mediastinum. To mitigate this risk, we suggest implanting oversized pulmonary homografts (28 mm or larger) and administering oral non-steroidal anti-inflammatories for the first 6–12 postoperative months.

Conclusion

In summary, the Ross procedure results in improvement of clinically relevant outcomes in non-elderly adults, namely survival, quality of life and a lower risk of valve-related complications. While the risk of reintervention has long been the main drawback of this procedure, recent evidence suggests the hazard of repeat surgery compares favorably to conventional AVR, especially in patients with aortic stenosis. Careful attention to surgical technique is a key factor for ensuring good long-term results after the Ross procedure.

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39

Bicuspid Aortic Valve and Aortopathy

Sri Harsha Patlolla and Hartzell V. Schaff

High Yield Facts

- Bicuspid aortic valve (BAV) is reported to have a prevalence of 1–2% worldwide and is the most common congenital heart anomaly in adults.
- Typically sporadic, it can also occur as an autosomal dominant inherited disorder with variable expression and reduced penetrance.
- A BAV may present in isolation or in association with additional congenital and genetic disorders with cardiovascular manifestations including patent ductus arteriosus, coarctation of the aorta, ventricular septal defects and syndromes such as Turner's, Loeys-Dietz, and Shone's complex.
- Aortic stenosis, the most common complication of BAV, has a reported incidence of 15–75% in these patients.
- 25% cases of infective endocarditis are said to develop on a BAV.
- Approximately 15% of BAV patients have dilatation of the ascending aorta at the time of diagnosis and by 20 years of follow-up almost 40% of patients will exhibit aortopathy.
- Although risk of aortic dissection is greater in patients with BAV compared to a normal population, overall incidence is low (3.1 per 10,000 patient years).
- In patients with BAV and no significant valve dysfunction, intervention on the aorta is recommended if the maximal aortic diameter exceeds 5.5 cm, provided the patient does not have additional high risk characteristics.
- The presence of risk factors such as aortic coarctation, systemic hypertension, family history of dissection, or rapid aortic growth may prompt an early surgical intervention at an aortic diameter of 5.0 cm.

Introduction

Bicuspid aortic valve (BAV) is reported to have a prevalence of 1–2% worldwide and is the most common congenital heart anomaly in adults [1–7]. Typically sporadic, it can also occur as an autosomal dominant inherited disorder with variable expression and reduced penetrance [8–10]. A BAV may present in isolation or in association with additional congenital and genetic disorders with cardiovascular manifestations [1, 11, 12] including patent ductus arteriosus, coarctation of the aorta, ventricular septal defects and syndromes such as Turner's, Loeys-Dietz, and Shone's complex among others [13–17].

A normally functioning BAV usually has no clinical manifestations but may be identified in association with other serious cardiovascular problems such as aortic aneurysms, aortic dissection or rupture [2, 11, 13, 18]. Though it may go undetected, many patients with BAV will develop complications and require intervention. In a study of asymptomatic patients with normally functioning or minimally dysfunctional BAV by Michelena et al., the reported incidence of cardiovascular events and surgical interventions after 20 years of follow up were 33% and 27% respectively (Fig. 39.1) [11].

Anatomy

A BAV has two cusps of unequal size generally due to fusion or non-separation of two cusps, and the malformation may include abnormalities of the aortic sinuses, ori-

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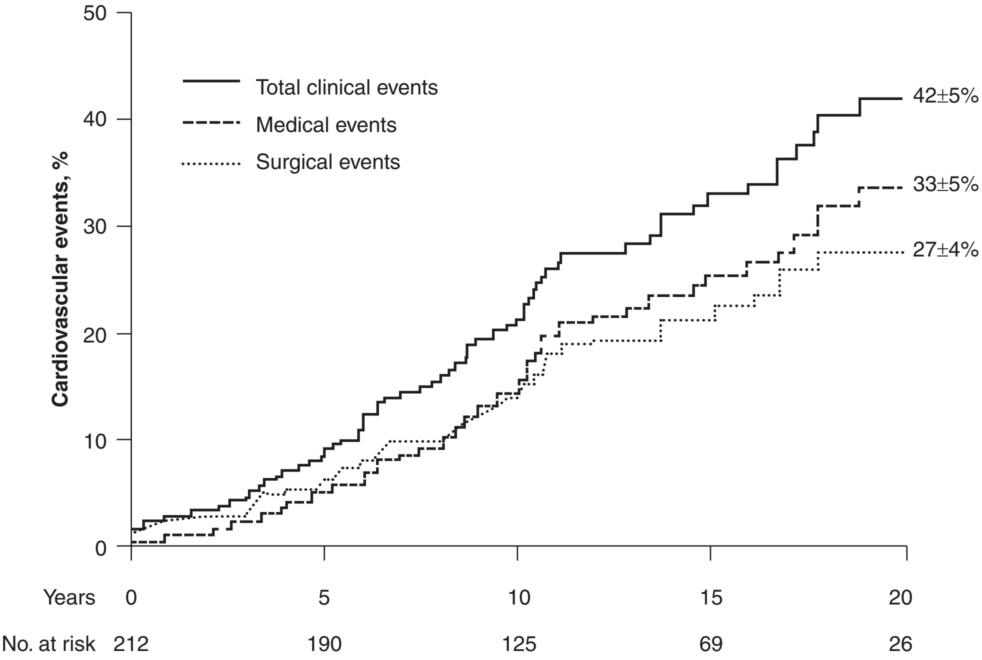

Fig. 39.1 Incidence of any cardiovascular event (total of medical or surgical; indicated by solid line), medical events (cardiac death, congestive heart failure, new cardiac symptoms, stroke, and endocarditis; indicated by dashed line), and surgical events (AVR, surgical valvotomy, ascending aorta surgery, or coarctation surgery; indicated by dotted line) in asymptomatic patients with BAV after 20 years of follow up. The event rates (±SE) at 20 years are indicated [11]. (Copyrighted and used with permission from American Heart Association, Inc.)

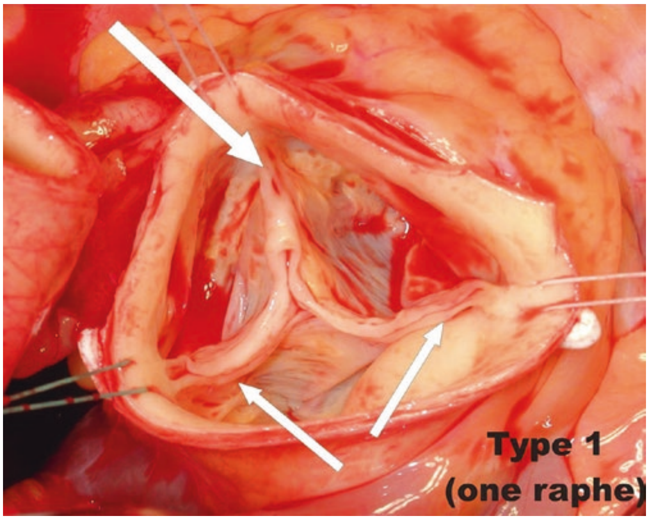

Fig. 39.2 Intraoperative picture of a type 1 bicuspid aortic valve with one completely developed noncoronary cusp, two completely developed commissures (small arrows), and one raphe between the underdeveloped left and right coronary cusps extending to the corresponding malformed commissure (large arrow) [21]. (Copyrighted and used with permission from The American Association for Thoracic Surgery)

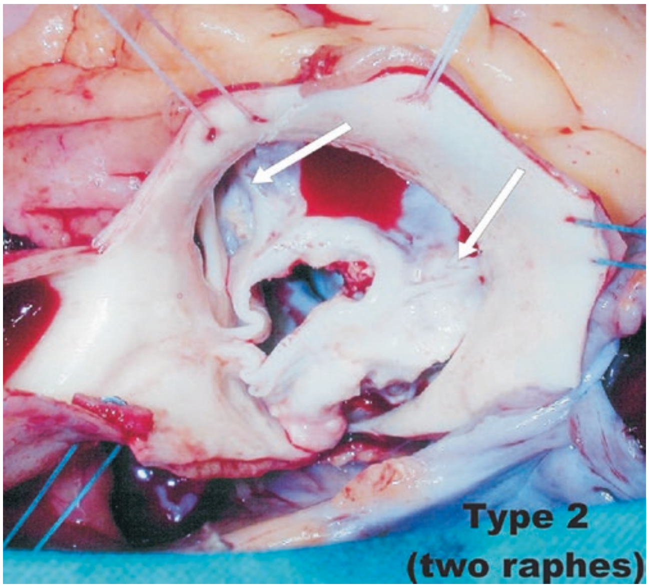

Fig. 39.3 Intraoperative picture of a type 2 bicuspid aortic valve, with two raphes (arrows) but developmental anlagen of three cusps with a high degree of stenosis [21]. (Copyrighted and used with permission from The American Association for Thoracic Surgery)

gins of the coronary arteries, and the aortic wall. There is often one larger cusp with a central raphe and smooth cusp margins [1, 19, 20]. Sievers and Schmidtke proposed a classification of BAV based on the presence and number of raphes with subtypes related to cusp orientation (Figs. 39.2, 39.3, 39.4) [21]. There can be partial or complete fusion between any of the cusps; however, the most common presentation is fusion of right and left cusps with an anterior-posterior orientation of the valve commissures which was found in 86% of patients reported by Sabet et al. [22]. The second most common anatomical type (12%) is the atypical pattern with fusion of right and noncoronary cusps with a single cusp beneath the left aortic sinus. The least common pattern is the fusion of the left and noncoronary cusps. Rarely, the cusps are symmetrical with no raphe [19].

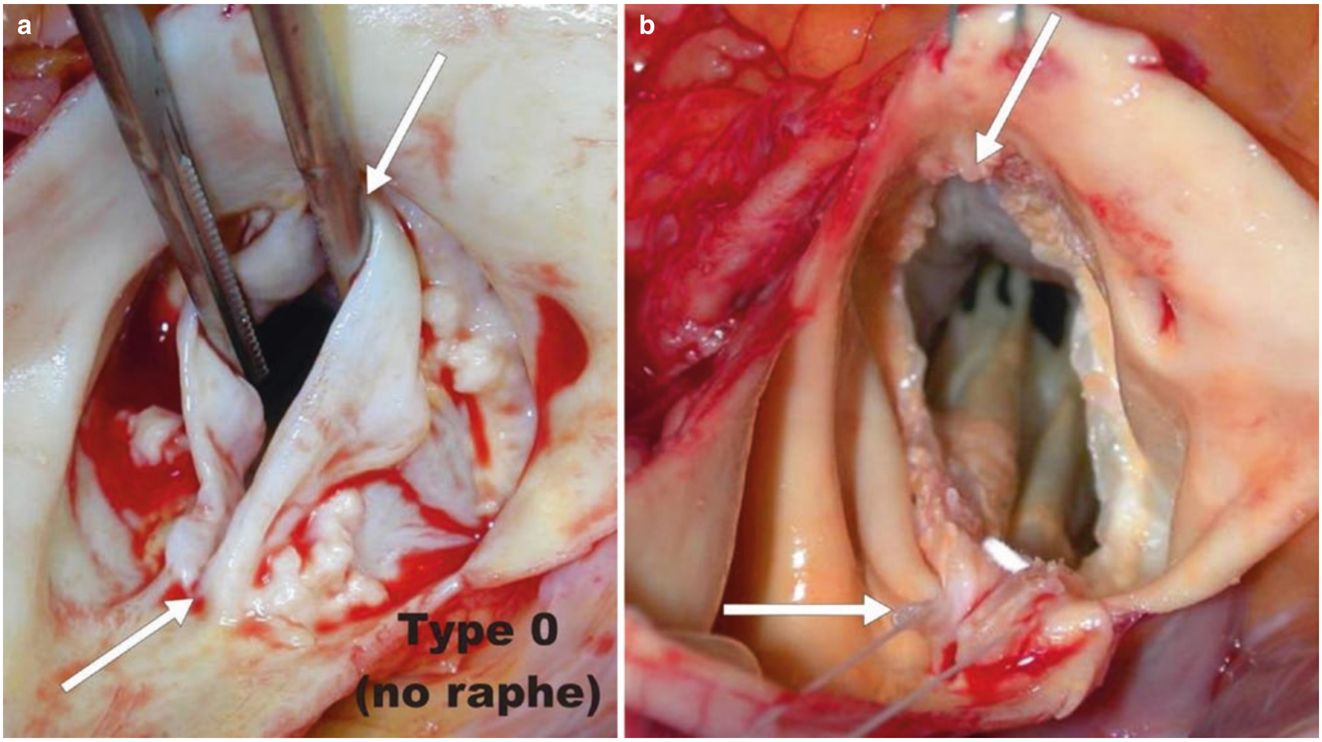

Fig. 39.4 Intraoperative picture of a "purely" bicuspid aortic valve, type 0, with two equal-sized cusps, no raphe, lateral arrangement of the free edge of the cusps, and presenting predominantly with stenosis. Note that there are only two commissures (arrows). Panel **a** shows the valve before excision and Panel **b** shows the valve after excision [21]. (Copyrighted and used with permission from The American Association for Thoracic Surgery)

Prevalence and Etiopathogenesis

In multiple studies the prevalence of BAV ranges from 0.5% to 2% with a 2:1 male to female ratio [1–7]. There is an even higher incidence of BAV in specific groups of population, for example approximately 50–75% of patients with coarctation of aorta and nearly 30% of females with Turner's syndrome have BAV [1].

The etiopathogenesis of BAV is unclear, but due to the frequent association of BAV with congenital malformations of other neural crest derived systems, abnormal migration of neural crest cells leading to fusion of valve cushions has been suggested [23, 24]. Deficiency of endothelial nitric oxide synthase which has a role in valve formation is another possible etiology [25, 26]. Extracellular matrix proteins like fibrillin-1 and fibulin play a role in cell differentiation and cusp formation during valvulogenesis and abnormalities in these proteins have also been implicated in BAV pathogenesis [2, 27].

Clinical Presentation

The clinical presentation of BAV is heterogeneous and depends on valvular function and presence of associated lesions or complications. Aside from infants with critical aortic stenosis, the disease is usually asymptomatic in the childhood. Adolescents and young adults may present with signs and symptoms of aortic regurgitation whereas stenosis due to calcification is the common manifestation in older adults.

Initial suspicion of a BAV is raised when routine physical examination reveals a murmur of aortic stenosis or regurgitation, and a normally functioning BAV often has an ejection click followed by a systolic murmur. In adults, the auscultatory findings depend on the degree of disease and associated complications. A harsher ejection murmur with late peaking is seen with progressive aortic stenosis. A diastolic decrescendo murmur, best heard at left lower sternal border, indicates presence of aortic regurgitation. An aortic regurgitation murmur that is loudest at the midsternal border may be suggestion of dilatation of ascending aorta. The physical examination of these patients should include arterial pulse examination along with auscultation for presence of coexisting diseases, such as coarctation of the aorta or ventricular septal defect.

Diagnosis

The diagnosis of BAV is established by transthoracic echocardiography (TTE) and distinctive features seen best in short-axis views include the characteristic two cusps with two commissures, cusp redundancy, presence of a raphe, and eccentric valve closure. Systolic doming and an eccentric valve closure are the findings in the parasternal long-axis views [1]. BAVs appear to open from the center and separate at the commissures in a curvilinear fashion whereas a normal tricuspid aortic valve maintains straight diastolic shape and pivot from point of annular insertion. This opening pattern is useful in identifying BAVs when cusps are poorly visualized. The sensitivity and specificity of TTE for identifying BAV are 78% to 92% and 96% respectively [28], but accuracy is lower when in the presence of stenosis or excessive calcification. A transesophageal echocardiogram can also be used to improve visualization of the cusps and aid in diagnosis in the absence of significant valvular calcification.

The echocardiographic evaluation of BAV should include assessment for valvular dysfunction and measurement of aortic diameters because of the frequent association with aortopathy. Additional imaging with cardiac magnetic resonance imaging (MRI) or computer tomography (CT) is recommended for complete assessment of the aortic root and ascending aorta.

Clinical Course and Complications

Studies have shown that the average life expectancy of asymptomatic or minimally symptomatic BAV patients after their initial diagnosis is similar to the general population despite increased risks of early aortic valve dysfunction, premature congestive heart failure, aortic valve replacement (AVR), endocarditis, thoracic aortic aneurysm formation etc. among other sequelae [11, 12].

Valvular Complications

Aortic stenosis (AS), the most common complication of BAV, has a reported incidence of 15–75% in these patients [1, 29]. Age dependent processes like fibrosis, stiffening and calcification of valves play a prominent role in the progression of the disease [3]. Smoking and hypercholesterolemia have also been suggested as risk factors for progression to severe aortic stenosis [30, 31]. The rate of progression of stenosis in BAV patients is higher than rate of progression in patients with tricuspid aortic valves. Further, patients with BAV undergo surgery for aortic stenosis 5–10 years earlier than those with tricuspid valves [32]. More detailed mechanisms of accelerated degeneration of BAV are not established but several hypotheses have been proposed.

Aortic regurgitation (AR) is a less common hemodynamic complication compared to valve stenosis, and some patients have both lesions. Regurgitation of a BAV usually presents at an earlier age compared to stenosis and is caused by fibrotic retraction of the conjoint cusp, cusp prolapse, dilatation of the sinus portion of the aorta, or to a combination of these abnormalities. Prior balloon valvuloplasty for BAV stenosis may also contribute to the development of AR.

In some reports, endocarditis develops in 2–3% of patients with BAV [11, 12], and 25% cases of infective endocarditis are said to develop on a BAV [33]. Infection can lead to cusp perforation or destruction causing severe AR with or without annular abscess.

Aortopathy

Aortopathy refers to dilatation of the ascending aorta and may include the sinus portion of the aorta (aortic root), the ascending aorta, and the aortic arch. In natural history studies, approximately 15% of BAV patients have dilatation of the ascending aorta at the time of diagnosis and by 20 years of follow-up almost 40% of patients will exhibit aortopathy [11]. The tubular ascending aorta is the most commonly involved segment and is seen in 60–70% of BAV patients with dilated aortas. Although dilatation of the ascending aorta may be present independent of valvular lesions, it usually occurs in the setting of BAV stenosis [34]. In patients with BAV, hemodynamic factors like turbulence in flow, increased aortic wall shear stress with higher flow velocities (Fig. 39.5) along with abnormalities within aortic wall like matrix disruption, smooth muscle cell loss contribute to the weakening of aortic wall resulting in aortic wall abnormalities [35–38]. Ascending aortic dilatation is considered a precursor for aortic dissection, and although risk of aortic dissection is greater in patients with BAV compared to a normal population, overall incidence is low (3.1 per 10,000 patient years) [39, 40].

Coarctation of the aorta has been reported in 6% of patients with BAV, and approximately 50–75% of patients with coarctation had BAV [4, 17, 20, 41]. Valve morphology may relate to the association of coarctation. BAV resulting from fusion of left and right coronary cusps had a higher frequency in patients with coarctation [13]. The BAV in these patients has been described as equally bicuspid with two symmetric sinuses of valsalva [1]. Though patients with both coarctation and BAV often undergo treatment at a young age, it is essential to have long term follow up as 11–14% of these require reoperation later in life. The presence of both these conditions together substantially increases the risk of aortic dissection and aneurysm [41–43].

Aortic dissection is the most serious complication of BAV aortopathy due to the associated high mortality rate. The risk of dissection increases with increase in degree of dilatation, and risk may also be increased in patients with hypertension related to associated coarctation of the aorta [3, 5]. The incidence of aortic dissection is five to ten times higher in patients with BAV when compared to those with a normal tricuspid aortic valve [5]. Dissection typically originates in the ascending aorta and involves the descending aorta.

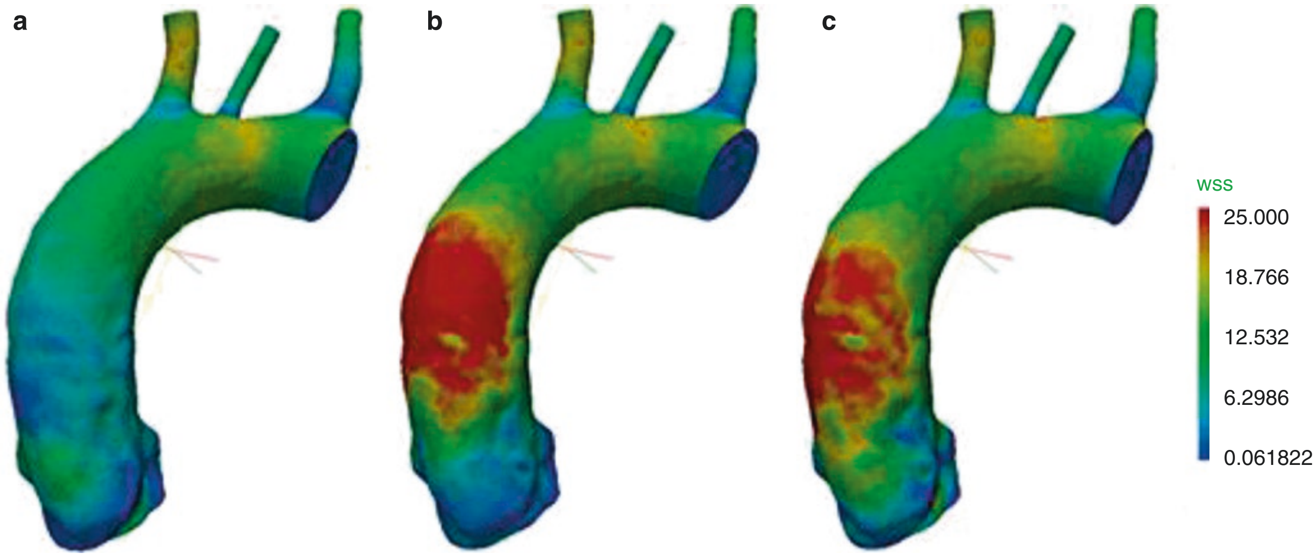

Fig. 39.5 Comparative finite element model analysis of ascending aortic flow in bicuspid and tricuspid aortic valve indicating wall shear stress (in dyne/cm^2) obtained in three valve models. (**a**) Tricuspid aortic valve (**b**) Bicuspid aortic valve (BAV) with right coronary and noncoronary cusp fusion (**c**) BAV with ideal fusion of right and left coronary cusps. The figure highlights the increased wall shear stress (red area) due the effect of asymmetric jet in BAV configurations compared to a tricuspid aortic valve [38]. (Copyrighted and used after modification with permission from International Center for Artificial Organs and Transplantation and Wiley Periodicals, Inc.)

Management

The principles of management of BAV are governed by the hemodynamic burden of valve dysfunction, risk of complications related to aortopathy, and the association with other congenital lesions. Depending on the presentation at diagnosis, the patients should have serial clinical and imaging assessments to identify the progression, development of complications, and timing of surgical intervention. Table 39.1 shows the guidelines recommendations for the surveillance and management of these patients using imaging techniques.

There is no evidence from clinical studies that medical therapy influences progression of valve dysfunction in patients with BAV. Some clinicians advocate use of beta blockers or angiotensin receptor inhibitors to regulate high blood pressure in order to reduce risk of complications from associated aortopathy. Because of the known risk of aneurysm formation and abnormal wall elastic properties,

Table 39.1 Guidelines recommendations for surveillance and management of patients with a bicuspid aortic valve[a]

Patients with BAV	Valve hemodynamics	Recommendation
Asymptomatic adolescents and young adults	Aortic valve mean Doppler gradient <30 mmHg or peak instantaneous gradient <50 mmHg	Doppler echocardiography every 2 years and an electrocardiogram (ECG) every other year.
	Aortic valve mean Doppler gradient >30 mmHg or peak instantaneous gradient >50 mmHg	Yearly Doppler echocardiography and a yearly electrocardiogram (ECG)
Older adults (>30 years of age) with aortic stenosis (AS)	Mild AS: peak jet velocity 2.0–2.9 m/s, mean gradient <25 mmHg	Doppler echocardiography every 3–5 years
	Moderate AS: peak jet velocity 3–3.9 m/s, mean gradient 25–40 mmHg	Doppler echocardiography every 1–2 years
	Severe AS: peak jet velocity ≥ 4 m/s, mean gradient >40 mmHg, valve area < 1.0 cm^2	Doppler echocardiography every 6–12 months
Adults of all ages with aortic regurgitation (AR)	Mild AR	Doppler echocardiography every 3–5 years
	Moderate AR	Doppler echocardiography every 1–2 years
	Severe AR	Doppler echocardiography every 6–12 months
Adults of all ages with bicuspid aortic valve	Aortic root or ascending aortic diameter >4.0 cm	Serial evaluation of the size and morphology of the aortic sinuses and ascending aorta by echocardiography, cardiovascular magnetic resonance, or computed tomography (CT) angiography, with the examination interval determined by the degree and rate of progression of aortic dilation and by family history

[a] Adapted from the ACC/AHA 2008 guidelines for the management of adults with congenital heart disease [44] and 2014 AHA/ACC guideline for the management of patients with valvular heart disease [45]

vigorous exercise, especially isometric exercise such as weight lifting, should be avoided. This is especially important for patients with BAV and previously repaired aortic dissection, those with moderately dilated aortas (>4.5 cm), and patients who have had a significant interval increase in aortic size. These activity restrictions should not limit aerobic or endurance exercise which can be helpful in blood pressure control. Patients with normally functioning BAV and no aortic dilatation may engage in normal physical activities.

Indications for surgery in patients with BAV depend upon the severity of associated AS or AR, valve phenotype, and accompanying aortopathy. The type of intervention depends upon whether the patients require aortic valve intervention or repair of aorta or both. In patients with no associated aortopathy, aortic valve repair or replacement is done when there is severe stenosis or regurgitation accompanying the BAV. According to 2008 ACC/AHA guidelines for the management of adults with congenital heart disease [44] and 2014 ACC/AHA valve guidelines [45] aortic valve replacement (AVR) is recommended for:

- Patients with severe AS and symptoms or left ventricular (LV) dysfunction (ejection fraction less than 50%)
- Adolescents or young adults with severe AR with symptoms or persistent LV dysfunction (ejection fraction less than 50%) and in those with severe AR with progressive LV dilatation (LV end-diastolic diameter ≥4 standard deviations above normal)

For patients with BAV and AR who require surgery, aortic valve repair may be a good option, and a number of techniques have been described [46–49]. In most patients with BAV, regurgitation is caused by retraction and/or prolapse of the conjoint cusp, and as mentioned previously, the most frequent anatomic configuration is a conjoint cusp beneath the right and left coronary sinuses. Most often BAV with prolapsing conjoint cusps are repaired by cusp plication or limited triangular resection and suture reconstruction of the median raphe with 5-0 or 6-0 suture (Fig. 39.6). This maneuver shortens and elevates the free edge of the cusp, increasing the area of coaptation and permitting apposition with the noncoronary cusp. Subcommissural annuloplasty is usually

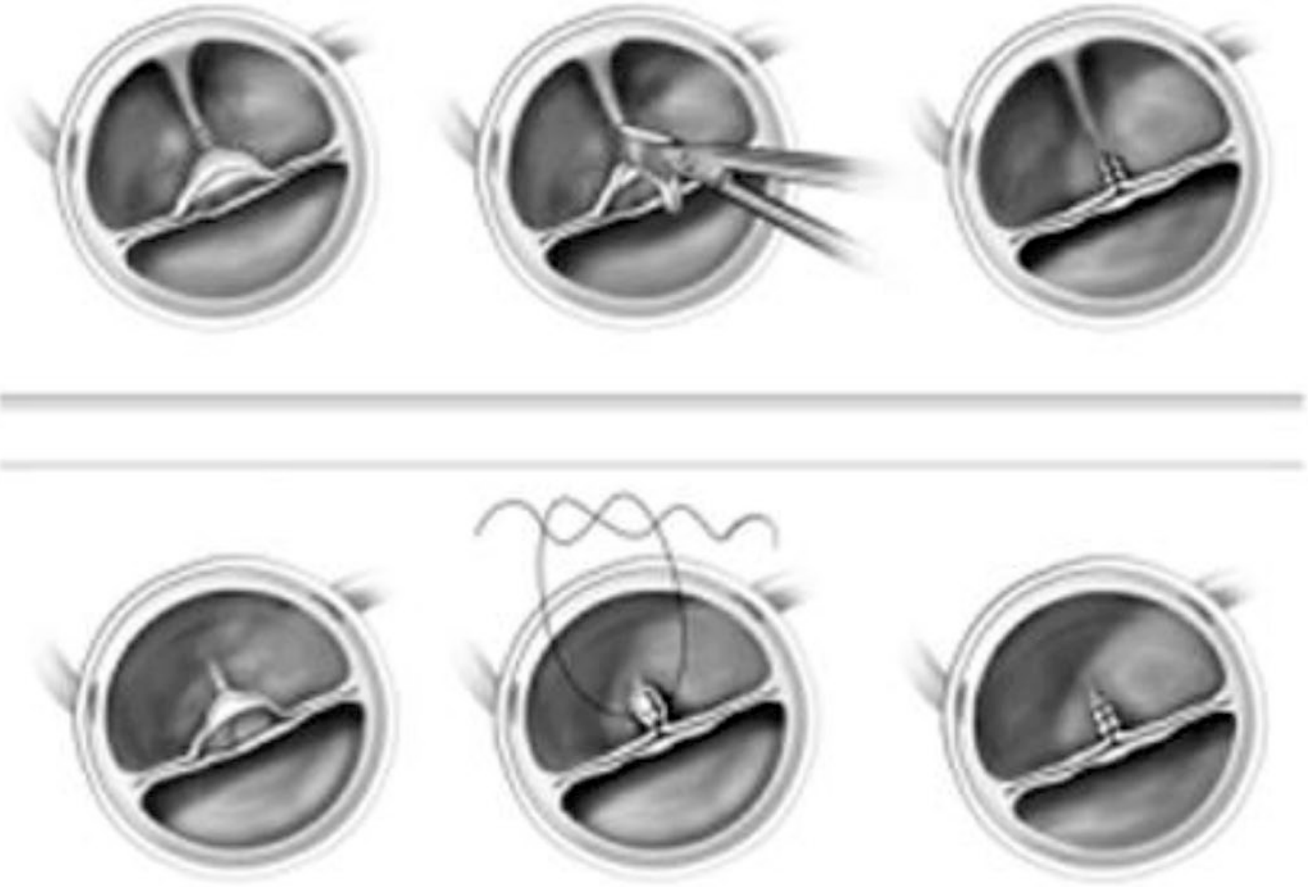

Fig. 39.6 Bicuspid aortic valve repair technique: Triangular resection of the conjoint cusp raphe is performed and then reconstructed using monofilament suture, with mid-cusp plication of prolapsing bicuspid aortic valve cusp without raphe [49]. (Copyrighted and used with permission from The American Association for Thoracic Surgery)

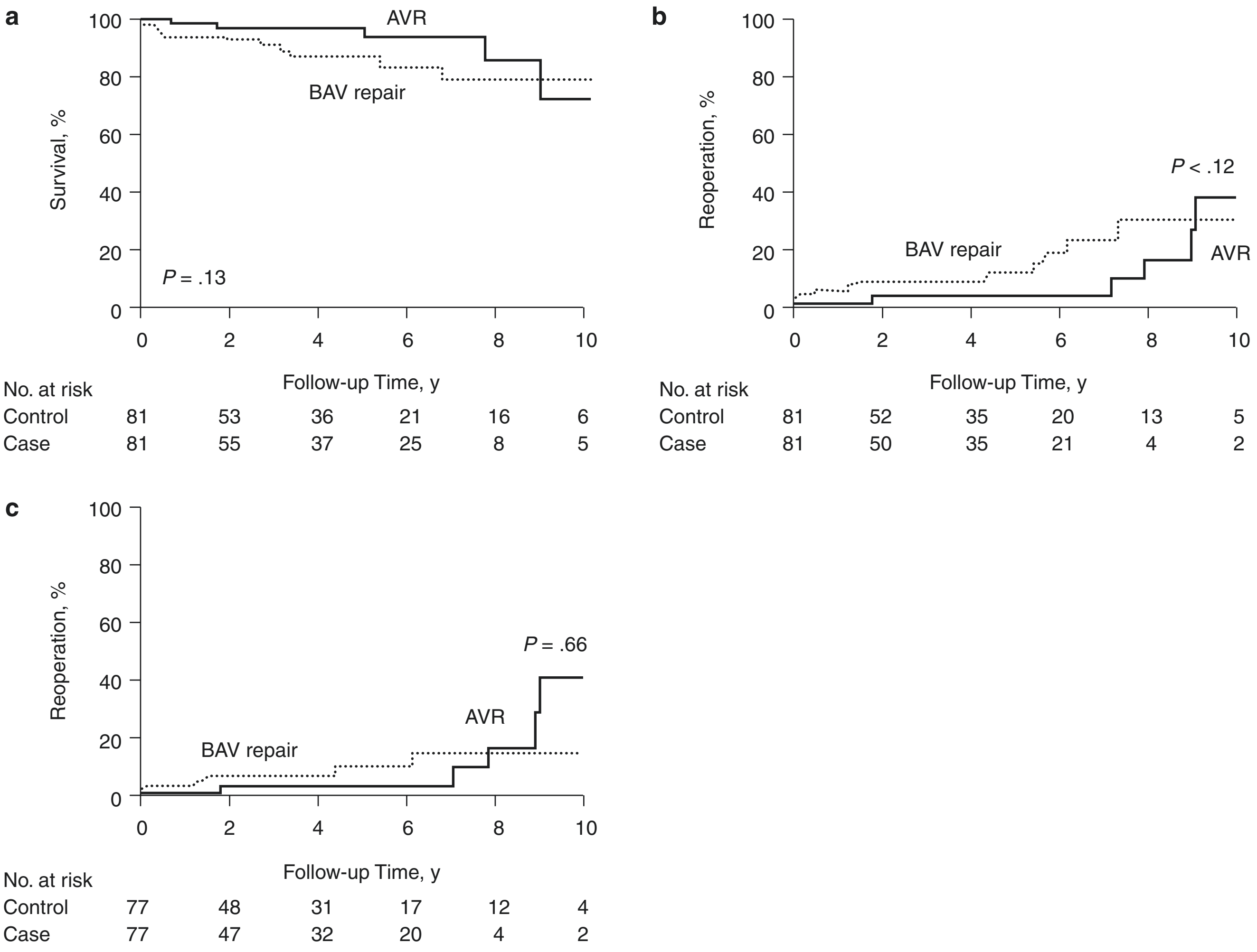

Fig. 39.7 Survival and risk of reoperation in matched groups after bicuspid aortic valve (BAV) repair and aortic valve replacement (AVR) with a bioprosthesis. (**a**) Survival of patients after BAV repair matched to patients who underwent AVR with a bioprosthesis. (**b**) Risk of reoperation in matched patients who underwent BAV repair or AVR with a bioprosthesis. (**c**) Risk of reoperation in matched patients who underwent BAV repair or AVR with a bioprosthesis after exclusion of patients and their matched pairs who underwent reoperation for indications not related to BAV repair failure [50]. (Copyrighted and used with permission from The American Association for Thoracic Surgery)

combined with cusp repair to narrow an enlarged annulus and improve central coaptation. The procedure has low operative mortality (<1%), and late durability equals or exceeds that of stented heterograft prostheses (Fig. 39.7) [50]. Patients should be counselled, however, that late reintervention will likely be necessary due to calcific degeneration and stenosis.

Aortic valve replacement remains the mainstay of treatment for severe AS and symptomatic severe AR as described in the indications above. Most patients with indications for valve replacement undergo surgical AVR through a median sternotomy, a partial upper sternotomy, or a parasternal intercostal incision. Presence of a BAV in a patient with aortic valve stenosis is generally considered to be a contraindication to transcatheter aortic valve replacement (TAVR), but several reports indicated that TAVR can be used successfully in carefully selected patients [14, 51–54]. In patients with severe native AR, surgical AVR is preferred as TAVR is still being investigated due to limitations such as insufficient anchoring of the transcatheter heart valve within the noncalcified aortic annulus and the risk of residual AR [55].

Along with the decision regarding choice of procedure for valve replacement, the choice of prosthetic heart valve also plays an important role in patient outcomes. The factors that impact the choice of a mechanical valve or bioprosthetic valve are summarized in Table 39.2 [45, 56].

Current mechanical valve options are the bileaflet St. Jude, Carbomedics and On-X valves. Bioprosthetic aortic valve options include bovine pericardial and porcine xenografts along with aortic homografts and the pulmonary autograft in aortic position (Ross procedure). In general, we

Table 39.2 Factors impacting choice of prosthetic valve

Mechanical valve
• Age <50 years
• Low risk of long term anticoagulation
• Presence of an additional indication for anticoagulation (e.g. an existing mechanical valve, atrial fibrillation)
• High risk of morbidity/mortality with reintervention
Bioprosthetic valve
• Age >70 years
• If the expected effective longevity of a bioprosthetic valve is greater than patient's life expectancy
• High risk of long term anticoagulation
• Patient desire to avoid risk and inconvenience of anticoagulation

reserve use of aortic homograft valves for patients with native or prosthetic valve endocarditis who require annular reconstruction [57, 58].

Choice of bioprostheses or mechanical prostheses for patients with BAV <65 to 70 years rests largely on patient preference. The current generations of mechanical valves are durable and have relatively low risk of thromboembolism. Indeed, risk of thromboembolic complications following AVR with a bioprosthesis is not different from risk in anticoagulated patients with a mechanical prosthesis. Despite limitations of available evidence, a few studies have shown similar early mortality rates after surgical valve replacement with aortic bioprosthetic and mechanical valves [59]. Results on long term mortality have been mixed, but some studies have found lower mortality rates with a mechanical valve in younger age groups [59–61].

In theory, the Ross procedure is an excellent choice for a young patient with BAV who requires AVR, and selected series from centers with surgeons experienced in the method report low early mortality and excellent freedom from valve-related complications [62–64]. There are, however, additional potential hazards in the Ross procedure compared to standard AVR, and late reoperations can be complex [65, 66].

Aortic Root and Ascending Aorta Surgery

The issue of timing of intervention for aortopathy in patients with BAV is complex and involves multiple considerations. Primarily, the risk of aortic surgery must be weighed against the risk of subsequent aortic dissection and rupture. Although aortic events are related to aortic size, risk is not predicted by aortic diameter alone. Other factors influencing timing of intervention on the aorta in a patient with BAV and aortopathy include valve dysfunction (stenosis and/or regurgitation), rate of aortic enlargement, BAV phenotype, patient age, family history, associated conditions like coarctation or connective tissue disorders as well as anticipated operative risk and overall prognosis.

Indications in Patients with BAV Without Significant Aortic Valve Dysfunction

In patients with BAV and no significant valve dysfunction, intervention on the aorta is recommended if the maximal aortic diameter exceeds 5.5 cm, provided the patient does not have additional high risk characteristics [67]. The cut-off of aortic diameter at which frequency of dissection increases to a level that outweighs anticipated mortality and morbidity of repair is unknown [39]; it should be mentioned that, dissection can occur in patients with BAV in whom aortic size is near normal. Current recommendations are based on the observation that regardless of valve morphology 6.0 cm represents a definite inflection point in the risk of aortic complications in all patients [68]. More recent evidence supports elective aortic replacement at a smaller dimension. Zafar and associates suggest that there may be two inflection points signaling increased risk of dissection, one at 5.25 cm and the other at 5.75 cm (Fig. 39.8) [69]. Data from these studies that estimate risk of dissection based on aortic size include patients with tricuspid and bicuspid valves, and it is reasonable to assume that risk is equal or greater in patients with BAV.

The presence of risk factors such as aortic coarctation, systemic hypertension, family history of dissection, or rapid aortic growth may prompt an early surgical intervention at an aortic diameter of 5.0 cm. Similarly, patients with Turner syndrome and/or short stature should be considered for aortic repair at lower aortic dimensions depending on the recommended indexed aortic diameters [70, 71]. Due to the increased risk of aortic complications in pregnancy, aortic repair may be considered at diameter of 5.0 cm in women planning pregnancy [72]. Recent studies have suggested a higher risk of adverse aortic events in patients with AR and root phenotype of aortic dilatation compared to those with AS [73–76], thereby suggesting the requirement of an early intervention at an aortic diameter of 5.0 cm in these patients.

For patients with BAV and enlargement of the ascending aorta and aortic root, valve sparing procedures may be indicated. Valve sparing aortic root surgery includes David (reimplantation technique) and Yacoub (remodeling technique) and both methods have been used in patients with BAV. There is debate regarding patient selection and advisability of BAV preservation when cusp repair for AR is necessary.

Indications for Aortic Replacement in Patients with BAV and Aortic Valve Dysfunction

The threshold for replacement of the ascending aorta in patients with BAV undergoing valve surgery is much reduced because the patient is exposed to general risks of heart surgery. Although decisions must be individualized, the recommended cutoff for concomitant ascending aortic replacement is 4.5 cm [45, 77, 78]. This recommendation is based on studies suggesting an increased risk for subsequent aortic dissec-

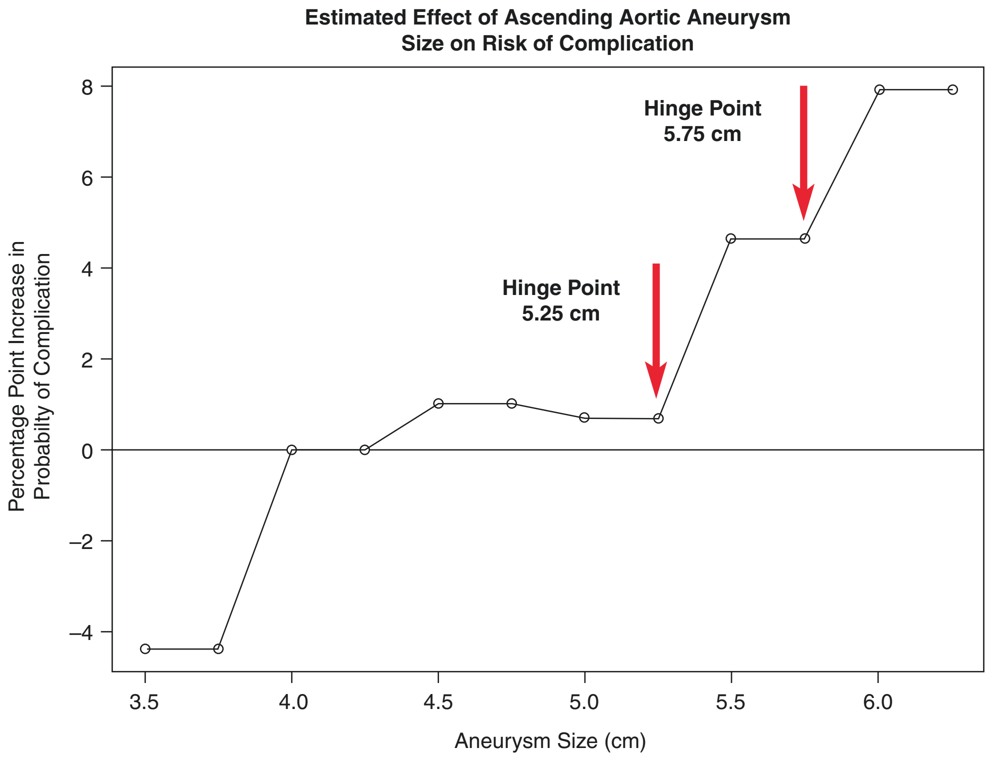

Fig. 39.8 Figure shows the estimated probability of rupture or dissection of the ascending aorta by aneurysm size [69]. (Copyrighted and used with permission from The American Association for Thoracic Surgery)

tion in BAV patients undergoing AVR with an aortic diameter of more than 4.5 cm [79, 80]. Table 39.3 shows the guidelines recommendations for interventions on aorta in patients with bicuspid aortic valve and associated aortopathy.

A prosthetic aortic valve and a supracoronary aortic Dacron graft are placed in patients who require aortic valve replacement and have ascending aortic dilatation above the sinotubular junction. A composite aortic valve and ascending aorta graft replacement is performed in patients who require aortic valve replacement and have dilated aortic roots and ascending aortas. Patients with BAV undergoing AVR usually do not require aortic root replacement, but composite replacement is recommended in patients with a sinus dimension exceeding 4.5 cm [11, 79, 81]. Root replacement is often necessary in patients with BAV presenting with acute aortic dissection, because the sinus portion is frequently involved [82]. Often there is asymmetrical configuration of the sinus portion of the aorta in patients with BAV with predominant enlargement of the noncoronary sinus. In such patients the ascending aorta and noncoronary sinus can be replaced without mobilization and reimplantation of the coronary ostia [83].

In BAV patients with aortopathy and an anticipated high operative mortality, performing ascending aortic replacement alone and sparing a modestly dilated root is often the safest approach [84]. Subsequent dissection or rupture of the sinus portion of the aorta is very uncommon in patients with BAV undergoing AVR and replacement of the ascending aorta [85, 86].

Table 39.3 Guidelines recommendations for aortic replacement in patients with bicuspid aortic valve aortopathy[a]

Patient characteristic	Recommendation	Class of recommendation
Patients without risk factors	Repair of the ascending aorta/root when aortic diameter is ≥55 mm	I
Patients with risk factors (root phenotype, uncontrolled hypertension, family history of aortic dissection/sudden death, coarctation, aortic growth>3 mm/years)	Repair of the ascending aorta/root should be performed when aortic diameter is ≥50 mm	IIa
Patients at low surgical risk and operated on by an experienced aortic team in a center with established surgical results	Repair of the ascending aorta/root may be performed when aortic diameter is ≥50 mm	IIb
Patients undergoing cardiac surgery	Concomitant repair of the ascending aorta/root when aortic diameter is ≥45 mm	IIa
Patients with aortic arch diameter of ≥55 mm	Repair of aortic arch	I
Patients undergoing cardiac surgery	Concomitant repair of aortic arch if aortic arch diameter is ≥50 mm	IIa

(continued)

Table 39.3 (continued)

Patient characteristic	Recommendation	Class of recommendation
Patients undergoing cardiac surgery and at low surgical risk and operated on by an experienced aortic team with established surgical results	Concomitant repair of aortic arch may be performed if the aortic arch diameter is ≥45 mm	IIb
Patients undergoing elective aortic arch repair	Should be referred to an experienced aortic team with established surgical results	I

[a]Adapted from 2018 AATS consensus guidelines [67]. (Copyrighted and used with permission from The American Association for Thoracic Surgery)

Aortic Arch

There is a lack of evidence on the natural history of aortic arch and aortic arch pathologies in patients with BAV. Indeed, there is debate amongst surgeons on the need for extending aortic resection into the arch in BAV patients undergoing ascending aortic replacement [87, 88]. In a study of 422 patients with BAV undergoing replacement of the ascending aorta without intervention on aortic arch, Park et al. found no late deaths due to dissection and no patient had reoperation for progressive arch enlargement. The authors recommended tailoring the extent of distal aortic arch operation in patients with BAV and avoiding arch repair if transverse arch is not larger than 4.5 cm [89]. The AATS consensus guidelines have made the following recommendations for the management of aortic arch in BAV patients:

- Ascending aortic repair without arch intervention is recommended in patients presenting for AVR with BAV and an ascending aortic aneurysm with a normal aortic diameter below the takeoff of the innominate artery.
- Hemiarch replacement is reasonable, if the aortic arch has a diameter of greater than 4.5 cm at the innominate artery takeoff, in experienced centers, with the understanding that operative mortality and risk of stroke may be minimally increased.
- A total arch replacement is reasonable in patients with BAV undergoing AVR with a mid-aortic arch diameter of 4.5 cm or greater at the level of left carotid artery as measured by 3D aortic centerline reconstructions.

Contemporary data have shown an association between operative mortality and hospital and surgeon volume in patients undergoing thoracic aortic surgery [90]. They found improved outcomes in young patients (<65 years age) as well as in high risk patients with increased hospital volume. Another study comparing low volume centers with high volume centers found an increased mortality in low volume centers for isolated ascending aneurysms and arch aneurysms [91]. These suggest the importance of referring patients requiring extensive aortic repair involving arch to tertiary referral centers with expertise in aortic diseases.

Postoperative Surveillance

Establishing a baseline for future comparisons and identifying anastomotic pseudoaneurysms are the primary objectives of aorta imaging soon after surgery.

We obtain transthoracic echocardiograms before hospital dismissal in all BAV patients who have operation and additional CT angiograms are obtained in those who have aortic replacement. The frequency and intervals of subsequent imaging after aortic surgery are determined by the extent of the initial procedure. Patients who have undergone AVR without aortic repair should be followed with yearly echocardiograms as recommended by the 2013 STS guidelines. CT or MRI every 3–5 years after repair is recommended in the presence of residual aortic dilatation or pathology. In adolescents and adults <50 years MRI should be considered for repeat examinations for post-surgical surveillance to minimize X-ray exposure.

Summary

BAV disease is complex due to valvular involvement and consideration of associated aortopathy. Patients often present at a relatively young age which further complicates clinical decision making regarding timing of valve surgery, choice of prosthesis, and aortic intervention. Every cardiac surgeon should be well versed in the pathology and pathophysiology of BAV disease and should understand the areas of controversy that we have highlighted in this chapter.

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Mitral Valve Replacement

David Blitzer, Jeremy J. Song, and Damien J. LaPar

High Yield Facts

- There are approximately 12 million cases of rheumatic heart disease (RHD) worldwide. In Europe 12–22% of all valvular heart disease is attributed to RHD, while this number is just 0.1% in the United States.
- Severe mitral regurgitation is defined by an effective regurgitant orifice ≥0.2–0.4 cm^2, with a threshold of 0.2 cm^2 being more sensitive for severe regurgitation and 0.4 cm^2 being more specific. A regurgitant volume ≥60 mL is also used to define severe mitral regurgitation
- Severe mitral stenosis is defined by a mitral valve area ≤1.5 cm^2 which generally corresponds to a transmitral gradient of >5–10 mm when the heart rate is within the normal range
- Overall, mitral valve repair remains the preferred, initial operative approach, for the majority of mitral valve disease, particularly for mitral regurgitation
- Chordal sparing mitral valve replacement plays an important role in preserving left ventricular function and limiting the incidence of perforation or atrioventricular dissociation with mitral valve replacement.
- The most common surgical approach to the mitral valve is via a left atriotomy after development of Sondergaard's groove.
- There is a 44% failure rate in bioprosthetic valves versus a 4% failure rate in mechanical valves in patients under 65 years old with no significant difference in all-cause mortality
- Mechanical valves have a 1–2% annual rate of thromboembolic events compared to 0.7% per year for bioprosthetic valves.
- Current AHA/ACC class IB recommendations for mechanical valves suggest lifelong aspirin and warfarin for a target International Normalized Ratio (INR) of 2.5–3.5. For bioprosthetic valves, the current class IIa recommendations call for warfarin with target INR of 2.5 for first 3 months unless they require warfarin for other reasons.

Introduction

The surgical management of mitral valve disease is increasingly common for the contemporary cardiac surgeon. Mitral valve pathology is organized by etiology into four main categories: degenerative, ischemic, rheumatic, or infectious (endocarditis). Each of these etiologies can result in stenosis and/or regurgitation at the valvar and/or subvalvar level. The specific characteristics of valve dysfunction are critical to guiding the surgical management.

Chronic mitral regurgitation (MR) can be characterized as resulting from a primary or secondary process. Chronic primary regurgitation results from degeneration at the level of the valve, and repair of such a valve is often considered the optimal surgical procedure. Chronic secondary regurgitation, or functional regurgitation, occurs as a result of left ventricular (LV) dysfunction, generally due to coronary artery disease, myocardial infarction, or another cause. In the case of functional regurgitation, the valve itself is normal; however, LV dysfunction results in secondary valvular dysfunction. Severe MR is defined by echocardiographic evidence of an effective regurgitant orifice ≥0.2–0.4 cm^2, with a threshold of 0.2 cm^2 being more sensitive for severe regurgitation and 0.4 cm^2 being more specific, as well as a regurgitant volume ≥60 mL [1].

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Worldwide, rheumatic heart disease (RHD) remains a significant etiologic factor for development of mitral stenosis (MS). RHD results from rheumatic fever as either a child or young adult, occurring more commonly among females [2]. There are approximately 12 million cases of RHD worldwide, for an estimated prevalence of 20–35 per 100,000 [3]. While more prevalent worldwide, rheumatic valve disease is less common in developed countries where aggressive treatment and screening have diminished its prevalence. In Europe, 12–22% of all valvular heart disease is attributed to RHD, while the prevalence within the U.S. is approximately 0.1% [4–6]. Severe MS is defined by echocardiographic measurements of a mitral valve area ≤1.5 cm^2, which generally corresponds to a trans-mitral gradient of >5–10 mm [1].

Repair Versus Replacement

The decision to repair or replace a mitral valve is influenced by multiple factors, including mechanism of valve dysfunction, primary etiology, cardiac function and status, and surgeon experience. Surgical intervention is recommended by the American Heart Association/American College of Cardiology (AHA/ACC) for severe MR which is acute and symptomatic or chronic with NYHA class II, III, or IV symptoms (Table 40.1). Surgical preference generally favors mitral valve repair over replacement when feasible as it has been demonstrated to confer a survival benefit [7, 8]. For most cases of severe MR, mitral repair is possible. However, for some cases in the setting of RHD, a calcified & fibrosed valve, extensive leaflet destruction, or endocarditis, which can also result in extensive valve destruction, mitral valve replacement (MVR) may provide a more durable option. In the case of chronic severe ischemic MR, a landmark randomized clinical trial by the Cardiac Surgical Trials Network (CTSN) compared mitral valve repair and chordal sparing MVR. This study demonstrated no significant difference in the primary outcomes of LV end-systolic volume index (z score, 1.33; P = 0.18) or in the incidence of cardiac or cerebrovascular events. Importantly, there was a significantly decreased recurrence rate of moderate or severe MR in the MVR group compared to the repair group (32.6% vs. 2.3%, P < 0.001) [9]. These results challenged established practice patterns favoring mitral valve repair for ischemic MR.

MVR remains the procedure of choice for MS. Current AHA/ACC guidelines recommend MVR for patients with moderate MS (mean valve area ≤1.5 cm^2) and NYHA class III/IV symptoms that is not amenable to balloon dilation (Table 40.2) [1]. In addition, MVR is indicated for symptomatic, severe MS (mean valve area ≤1.0 cm^2).

Table 40.1 American Heart Association/American College of Cardiology (AHA/ACC) recommendations and indications for surgical mitral valve replacement in mitral regurgitation

Indication	Class of recommendation	Level of evidence
Primary mitral regurgitation		
Symptomatic patients with chronic severe primary MR (ERO ≥0.20 cm^2; Regurgitant volume ≥30 cc) and LVEF >30%	I	B
Asymptomatic patients with chronic severe primary MR and LV dysfunction (LVEF 30–60% and/or LVESD ≥40 mm)	I	B
When surgical treatment is indicated for patients with chronic severe primary MR limited to the posterior leaflet (repair preferred)	I	B
When surgical treatment is indicated for patients with chronic severe primary MR involving the anterior leaflet or both leaflets (repair preferred)	I	B
Chronic severe primary MR with other cardiac surgery indication	I	B
Asymptomatic patients with chronic severe primary MR with preserved LV function (LVEF >60% and LVESD <40 mm) with low expected mortality (repair preferred)	IIa	B
Asymptomatic patients with chronic severe nonrheumatic primary MR and preserved LV function with new onset of AF or resting pulmonary hypertension (PA systolic arterial pressure >50 mmHg) (repair preferred)	IIa	B
Chronic moderate primary MR (ERO <0.20 cm^2; Regurgitant volume <30 cc) with other cardiac surgery indication	IIa	C
Symptomatic patients with chronic severe primary MR and LVEF 30%	IIb	C
Rheumatic mitral valve disease (repair preferred)	IIb	C
Percutaneous MV repair may be considered for severely symptomatic patients (NYHA class III–IV) with chronic severe primary MR, a reasonable life expectancy, but prohibitive surgical risk	IIb	B
Secondary mitral regurgitation		
Chronic severe secondary MR (ERO ≥0.20 cm^2, regurgitant volume ≥30 cc) who are undergoing CABG or AVR	IIa	C
Severely symptomatic patients (NYHA class III–IV) with chronic severe secondary MR	IIb	B
Chronic moderate secondary MR with other cardiac surgery indication	IIb	C

AF atrial fibrillation, *AVR* aortic valve replacement, *CABG* coronary artery bypass grafting, *ERO* effective regurgitant orifice, *LVEF* left ventricular ejection fraction, *LVESD* left ventricular end-systolic dimension, *MR* mitral regurgitation, *MV* mitral valve, *NYHA* New York Heart Association, *PA* pulmonary artery

Table 40.2 American Heart Association/American College of Cardiology (AHA/ACC) recommendations and indications for surgical mitral valve replacement in mitral stenosis

Indication	Class of recommendation	Level of evidence
Severely symptomatic patients (NYHA class III/IV) with severe MS (MVA <1.5 cm^2) without prohibitive risk for surgery	I	B
Severe MS (MVA ≤1.5 cm^2) with other cardiac surgery indication	I	C
Severely symptomatic patients (NYHA class III/IV) with severe MS (MVA ≤1.5 cm^2) with other cardiac surgery indication	IIa	C
Moderate MS (MVA 1.6–2.0 cm^2) with other cardiac surgery indication	IIb	C
Severe MS (MVA ≤1.5 cm^2) who have had recurrent embolic events while receiving adequate anticoagulation	IIb	C

MS mitral stenosis, *MVA* mitral valve area, *NYHA* New York Heart Association

Valve Selection

The ideal prosthetic mitral valve would offer the durability of a mechanical valve with the hemodynamic characteristics of patient's native valve such that lifelong anticoagulation would not be required. Considering that such prosthetic valve characteristics do not exist in the modern surgical era, patients and surgeons most commonly choose from amongst the currently available commercial mechanical or bioprosthetic valve options. Mechanical valves offer superior durability in comparison to bioprosthetic valves with studies demonstrating a 44% failure rate in bioprosthetic MVR versus a 4% failure rate in mechanical MVR in patients under 65 years old with no significant difference in all-cause mortality [10]. Mechanical valves, however, have increased risk of thromboembolic events, with a rate of 1–2% per year versus 0.7% per year in bioprosthetic valves [1]. Given the significantly higher risk of thromboembolic events for mechanical prostheses, patients receiving mechanical MVR require treatment with lifelong anticoagulation, which bears its own risk profile. As a function of long-term valve durability, mechanical MVR is generally recommended for patients younger than 65 as well as in any patient that will otherwise require long-term anticoagulation, such as those with atrial fibrillation. On the other hand, bioprosthetic valves are recommended for patients older than 65 and for patients hoping to avoid long-term anticoagulation, such as women of childbearing age.

The mechanical valves that are FDA approved and currently in use are mostly of a bileaflet design. This design was an improvement over initial ball-and-cage or monoleaflet designs because of improved hemodynamics, namely decreased turbulence and diastolic pressure gradients. The bileaflet valves that are currently available include the SJM Regent (Abbott Laboratories, Abbott Park, IL), Carbomedics Standard Mitral Valve (LivaNova, London, UK), Open Pivot Mitral Valve (Medtronic, Dublin, Ireland), and On-X (CryoLife Inc., Kennesaw, GA). The SJM Regent (Abbott Laboratories, Abbott Park, IL) is a commonly used valve with a design that allows for excellent hemodynamics even down to smaller sizes. In contrast, hemodynamics studies suggest that the Carbomedics bileaflet valve should be avoided in cases of small mitral valve orifice [11, 12].

Bioprosthetic mitral valves include porcine valves and bovine pericardial valves. Porcine valves are constructed from porcine aortic valves and are constructed to mimic the hemodynamic properties of that valve. Available porcine valves include the Hancock II (Medtronic, Dublin, Ireland), Perimount Theon (Edwards Lifesciences, Irvine, CA), Mosaic valve (Medtronic, Dublin, Ireland), and the Biocor bioprosthesis (Abbott Laboratories, Abbott Park, IL). These valves are generally constructed by stenting the valve leaflets and attaching the stent to a sewing ring. The different valve options differ in the profile of the stent, which impacts the valve's effective orifice area, and the treatment of the leaflets which impacts the stiffness of the leaflets and the tendency toward calcification over time. When studied in the mitral position, the durability of bioprosthetic valves at 5, 10, and 15 year is 100%, 78–86%, and 66%, respectively [13, 14]. Carpentier-Edwards (Edwards Lifesciences, Irvine, CA) also offers a bovine pericardial valve the Perimount Plus. While initial studies suggested pericardial valves offered limited durability compared to other bioprostheses, changes in the design and leaflet fixative have significantly improved flow dynamics and they are now similar to porcine valves in regard to structural valve degeneration.

Stentless valves are another category of available substitutes which include allograft or xenograft valves, biological tubular sleeves, and designs like the Quattro valve (Abbott Laboratories, Abbott Park, IL), which resemble the bileaflet valves but which incorporate chordal support by extension of the leaflet pericardium. These valves were developed as an attempt to mimic the complex function of the natural mitral valve with a replacement option that would not require lifelong anticoagulation. Initial concerns related to durability, particularly with the incidence of leaflet tearing, often necessitating reoperation. Combined with the relative complexity of their implantation, these valves remain less frequently used than commercially available bioprosthetic or mechanical replacement options [15].

The pulmonary autograft, or Ross II, is another replacement option which has been espoused as offering long-term durability without the need for long term anticoagulation. Similar to stentless valves, these characteristics are particularly important in low resource settings in which the frequent monitoring required for anticoagulation and the spectre of reoperative surgery are particularly onerous. The largest reported series of using a pulmonary autograft in the mitral position comes from Syria, where Kabbani and colleagues reported on 92 patients with mean follow-up of 60 months [16]. In their report, freedom from valve degeneration, reoperation, and general survival at 5 years were estimated at 93.4%, 94.2%, and 86.0% respectively. Just as with the standard Ross procedure for aortic valve replacement, the Ross II bears the disadvantage of being a two valve procedure for single valve disease. Further studies are required to validate the long-term durability of this replacement strategy in order to establish its role for the surgical treatment of mitral valve disease.

Surgical Technique of Mitral Valve Replacement

Preoperatively, patients should have appropriate arterial and venous vascular access, a urinary catheter, and often a pulmonary artery catheter for monitoring and management. Prophylactic intravenous antibiotic therapy is routine. Cardiopulmonary bypass cannulation consists of arterial and bicaval venous cannulation, often with moderate hypothermia and utilization of both antegrade and retrograde cardioplegia myocardial protection strategies. The mitral valve is most commonly exposed through a left atriotomy after development of Sondergaard's groove (Fig. 40.1). Alternatively, the mitral valve may be accessed through the dome of the left atrium, a biatrial incision, division of the superior vena cava, or through the atrial septum in a transseptal approach. A surgical view of the mitral valve is demonstrated in Fig. 40.2.

Mechanical valve prosthesis fixation is usually performed using an everting suture technique. The everting technique places annular interrupted, horizontal mattress, pledgeted

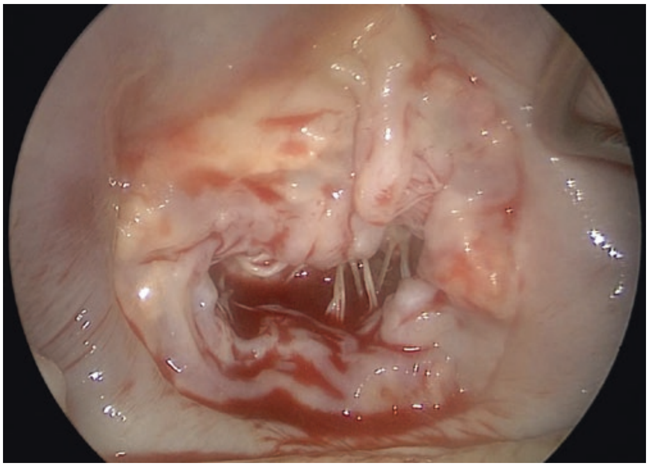

Fig. 40.2 Surgical view of the mitral valve

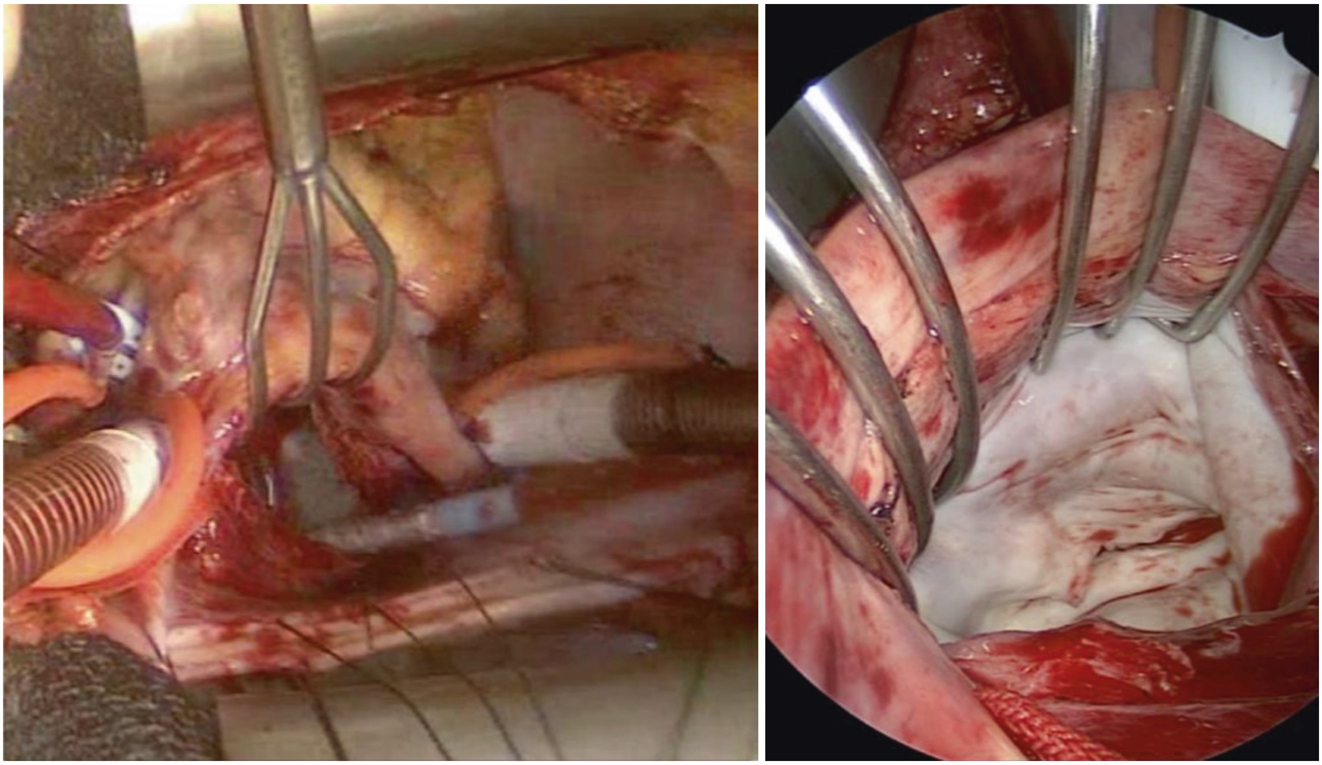

Fig. 40.1 Approach to the mitral valve through Sondergaard's groove

sutures that are passed from the atrium to the ventricle and then through the sewing ring of the valve prosthesis. The everting suture technique ensures a central position for the valve in relation to the valve orifice. In contrast, most bioprosthetic valves are secured using a non-everting suture technique, with annular sutures passed from the ventricle to atrium (Figs. 40.3 and 40.4). Importantly, for all valve implantations, it is critical to avoid injury to neighboring structures, most notably the circumflex coronary artery, the atrioventricular node, and the aortic valve leaflets that reside in close proximity to the anterior mitral curtain. Preservation of the subvalvular apparatus consisting of the chordal and papillary attachments to the mitral valve annulus plays an important role in preserving LV function and limiting the incidence of perforation or atrioventricular dissociation with MVR. A chordal sparing technique for MVR has been demonstrated to decrease the recurrence of moderate or severe MR at 12 months follow-up when compared to mitral valve repair [17]. While long-term comparisons have not yet been reported, these results have bolstered the role of chordal sparing MVR for the treatment of mitral valve disease.

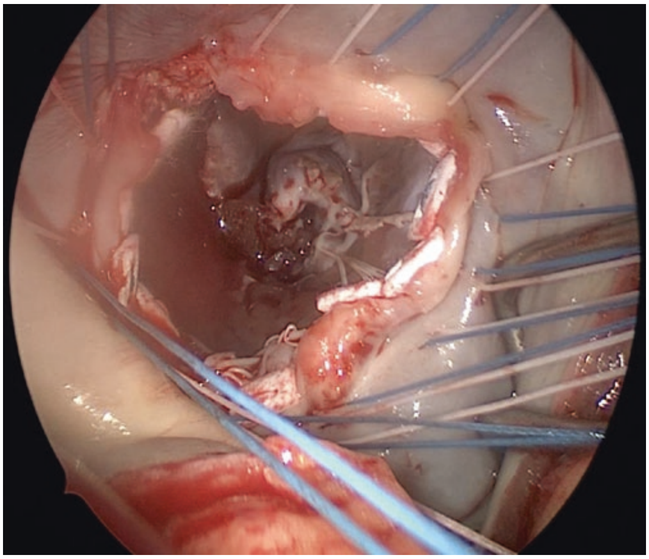

Fig. 40.3 Placement of inverting sutures around the circumference of the valve annulus

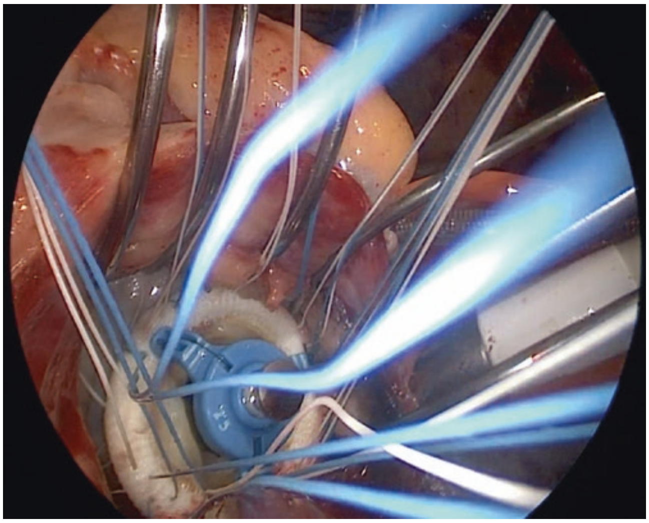

Fig. 40.4 Seating (positioning) of a bioprosthetic mitral valve

Following valve implantation, access atriotomies are closed, the left heart is de-aired, the aortic cross clamp is removed, and the patient is weaned from cardiopulmonary bypass (CPB). A transesophageal echocardiogram should be performed for all patients after cessation of CPB to evaluate the valve implantation, function, anatomic orientation, and for significant paravalvular leak.

Concomitant cardiac procedures are common at the time of MVR. Coronary artery bypass grafting (CABG) is the most common concomitant procedure performed with MVR. The surgeon must consider the operative sequencing of various cardiac procedures, especially when performing a MVR as significant manipulation of the heart after MVR should be avoided. Thus, in the setting of concomitant CABG, distal bypass graft anastomoses are performed first, followed by MVR, and then proximal graft anastomoses. For concomitant valve procedures, MVR is generally performed first. In the case of concomitant tricuspid valve procedures, the mitral valve can be approached through a transseptal approach. For concomitant aortic valve procedures, the aortic valve leaflets are generally excised first, MVR is completed, followed by aortic valve replacement.

More recently, advances have been made in minimally invasive and robot assisted MVR. The first series was reported in 1997 and included 11 patients undergoing MVR. In this comparison of conventional and minimally invasive (MIS) approaches, MIS patients were discharged earlier and incurred lower costs of hospitalization [18]. Complications among MIS patients included deep vein thrombosis and phrenic nerve palsy in one patient each. More recently, propensity matched studies comparing minimally invasive, robotic, and conventional mitral surgery have corroborated these early findings; however the vast majority of the minimally invasive procedures are valve repairs [19]. Central to the success of minimally invasive surgery is patient selection. The presence of significant comorbidities, multi-vessel coronary artery disease, or aortic valve or ascending aortic pathology are generally contraindications to a minimally invasive approach. Further specifics of surgical technique for minimally invasive MVR are beyond the scope of this chapter.

Surgical intervention also plays a key role in the management of both native valve endocarditis (NVE) and prosthetic valve endocarditis (PVE). Table 40.1 displays surgical indications for mitral valve endocarditis. For NVE, after exposure is achieved, extensive assessment for paravalvular abscess, intracardiac fistulae, or involvement of the intravalvular fibrous apparatus should be performed followed by radical resection of infected tissues. For NVE, repair can be attempted in the absence of extensive destruction [20]. For cases of PVE, the infected implanted valve is removed and extensive resection of infected tissues is performed. Following debridement, repair of valve annular structures must be performed to allow for valvular implantation. Repair strategies for NVE and PVE are multiple, including techniques to address the anterior and posterior leaflets, the annulus, the fibrous trigones, and the involvement of any neighboring structures. Post-operatively, all patients with NVE or PVE receive a minimum of 6 weeks of culture-directed antibiotic therapy regardless of mitral valve procedure.

Postoperative Management

Routine principles of early post-operative care of cardiac patients should be observed for all patients undergoing MVR. Patients with prosthetic mitral valve are usually anticoagulated in the immediate postoperative period given the high rates of arrhythmia [21]. Moreover, current AHA/ACC Class Ib recommendations for anticoagulation following mechanical MVR suggest lifelong aspirin and warfarin with a target International Normalized Ratio (INR) of 2.5–3.5 [1]. Generally, warfarin is started on postoperative day 2 with a low molecular weight heparin (LMWH) bridge until a target INR of 2.5–3.5 is achieved. For bioprosthetic valves, current AHA/ACC class IIa recommendations call for warfarin with a target INR of 2.5 for first 3 months [1]. After 3 months, anticoagulation can be discontinued unless the patient requires warfarin for other reasons such as the presence of a hypercoagulable condition, previous or existing thromboembolism, or persistent atrial fibrillation. Following bioprosthetic MVR, aspirin versus combined aspirin + warfarin therapy has been studied retrospectively in 25,000 patients >65 years old [22]. In these studies, combined antithrombotic therapy with aspirin + warfarin demonstrates a lower risk of death (Risk Reduction [RR] 0.80; 95%CI 0.66–0.96) and embolic events (RR 0.52; 95%CI 0.35–0.76) but with a significant higher risk of bleeding (RR 2.8; 95%CI 2.18–3.6) when compared to aspirin alone [1, 22–24].

Pregnancy presents a unique challenge for MVR management and warrants special consideration. In general, pregnant patients with mechanical prosthesis have a higher risk of valve thrombosis due to the relative hypercoagulability of pregnancy. In the second & third trimesters, the risk of thromboembolism can be managed with warfarin for a therapeutic INR and this is the current AHA/ACC Class I recommendation [1]. Warfarin, however, is contraindicated as a teratogen during the first trimester of pregnancy. As a result, current AHA/ACC Class IIa recommendation that warfarin therapy be continued if the therapeutic dose is 5 mg or less [1]. If the therapeutic dose is higher than 5 mg per day, dose-adjusted LMWH is substituted, with a target anti-Xa level of 0.8 U/mL to 1.2 U/mL which should be measured 4–6 h predose [1].

Future Directions

The availability of transcatheter interventions has transformed the management of aortic valve disease. Similarly, this strategy is an important future target for the management of mitral valve disease. Given the complex anatomy, the varied etiologies, and the success rates, there are many hurdles to technological development and widespread adoption of this strategy. Further, while there is no FDA approved transcatheter device available for mitral valve disease to date, there have been some successful reports for valve-in-valve replacement with the largest series utilizing the Intrepid valve (Medtronic Cardiovascular, Santa Rosa, CA, USA) with a 96% procedural success rate [25]. There was 8% and 14% mortality at 30 days and 4 months, respectively. Given the patient demand for minimally invasive interventions, it is almost a certainty that in the near future transcatheter management will play a prominent (if not predominant) role in the management of mitral valve disease.

Conclusions

The surgical management of mitral valve disease remains complex. While mitral valve repair techniques continue to evolve, recent clinical trials have challenged the presumed superiority of repair over replacement with respect to valve durability and freedom from reintervention. Continued technological advances in the design and composition of commercially available prostheses include mechanical, bioprosthetic and stentless bioprosthetic valves. A chordal sparing MVR technique has become standard surgical approach for MVR in the setting of functional and/or ischemic MR. Surgical approaches to MVR continue to expanded to include minimally invasive and robotic approaches. Transcatheter MVR remains on the horizon as an emerging approach to the treatment of mitral valve disease.

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Techniques for Mitral Valve Repair

41

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High Yield Facts

- Degenerative mitral valve regurgitation (MR) is the second most common valvular disease.
- MR most commonly ranges from a single prolapsing valve segment to diffuse myxomatous degeneration with bileaflet prolapse and annular dilatation.
- More than 90% of degenerative mitral valves are suitable for valve repair rather than replacement, with short and long term clinical outcomes being superior after repair.
- The 2017 ACC/AHA guidelines strongly recommend (class I) prompt surgical correction of MR for patients in stages D (severe symptomatic MR) and C2 (severe asymptomatic MR with left ventricular ejection fraction (LVEF) <60% or left ventricular end-systolic diameter (LVESD) >40 mm) and also include a new recommendation (class IIa) for early correction of MR in stage C1 patients (severe asymptomatic MR with LVEF >60% or LVESD <40 mm) if mortality risk is <1% and rate of repair is >95%.
- Mitral valve repair can be safely and effectively performed through sternotomy, anterolateral thoracotomy as well as robotic assisted procedures.
- A variety of repair techniques including triangular resection, quadrangular resection with sliding plasty, neochordae implantation coupled with annuloplasty are being used to achieve mitral valve repair with good mid- to long-term durability.

Introduction

Degenerative mitral valve regurgitation (MR) is the second most common valvular disease and most commonly ranges from a single prolapsing valve segment to diffuse myxomatous degeneration with bileaflet prolapse and annular dilatation [1, 2]. Mitral valve repair is preferred to replacement due to the reported benefits of lower operative mortality, higher durability, improved preservation of left ventricular function, and greater freedoms from prosthetic valve-related complications [3–5]. A variety surgical approaches (sternotomy, anterolateral thoracotomy, and robotic assisted procedures) and repair techniques have been developed over the last four decades to treat MR. In this chapter, we delineate different aspects of mitral valve repair techniques.

Patient Selection and Pre-operative Work-Up

Over the past decade, there has been growing evidence supporting early mitral valve repair in patients with severe asymptomatic MR and preserved cardiac structure and function [6–11]. Therefore, the 2017 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines strongly recommend (class I) prompt surgical correction of MR for patients in stages D (severe symptomatic MR) and C2 (severe asymptomatic MR with left ventricular ejection fraction (LVEF) <60% or left ventricular end-systolic diameter (LVESD) >40 mm) and also include a new recommendation (class IIa) for early correction of MR in stage C1 patients (severe asymptomatic MR with LVEF > 60% or LVESD <40 mm) if mortality risk is <1% and rate of repair is >95% [10].

Minimally invasive and robotic procedures are associated with rapid patient recovery and excellent safety and quality and offer similar costs compared to sternotomy operations at certain centers [6–9]. Minimally invasive mitral repair is appropriate for both degenerative and functional mitral valve

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disease. However, patients should be screened for comorbidities that may preclude safe application of this technique including intra-thoracic pathology, catheterization or computed tomography (CT) angiography, and carotid/peripheral vascular ultrasound/CT whenever it is applicable [12, 13]. Minimally invasive approaches mandate peripheral vascular access for cardiopulmonary bypass and atherosclerotic disease should be evaluated in elderly to prevent cerebral embolism or retrograde aortic dissection [14, 15]. Furthermore, severe sternal or thoracic deformities can compromise thoracoscopic or robotic instrument trajectories. Therefore, candidates should be evaluated by CT scan of the chest, abdomen and pelvis [13].

Finally, a transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE) study should be performed to confirm the diagnosis and determine the repair plan. TEE is also essential in the operating room to identify detailed mitral valve anatomy/pathology [13, 16].

Surgical Approaches

Sternotomy

Cardiopulmonary bypass is achieved with bicaval cannulation, with the inferior vena cava (IVC) cannula placed low down in the right atrium and the superior vena cava (SVC) cannula placed above the SVC and right atrial junction.

Robotic Approach

The patient is positioned at the right edge of the operating room table with a transverse roll under the chest. The right femoral artery and vein are exposed via an oblique incision above the groin crease and assessed for appropriateness for cannulation.

The endoscope camera port is placed in the fourth intercostal space (ICS), 2–3 cm lateral to the nipple. The working port incision is placed in the fourth ICS 4 cm lateral to the camera port. The left instrument port is placed two interspaces above and approximately halfway between the shoulder and the camera port. The right instrument port is two interspaces below and near the anterior axillary line. The fourth robotic port for the atrial retractor instrument is placed in the fourth ICS medial to the camera port.

A purse-string suture is placed in the anterior surface of the femoral vein and then a guidewire is passed through the femoral vein into the superior vena cava (SVC) under TEE guidance. A 25-Fr CardioVations "Quickdraw" venous cannula is passed over the wire and positioned so that the tip is several centimeters up the IVC. The femoral artery is cannulated using Seldinger technique. Cardiopulmonary bypass is initiated. The table is rotated all the way to the left and placed in reverse Trendelenberg. The da Vinci robot is brought to the surgical field and the arms and camera are positioned in the respective ports. Aortic occlusion is achieved using the transthoracic clamp (via a stab wound in the axilla) and cardioplegia is delivered antegrade and can be re-administered every 15–20 min throughout the cross-clamp time. The Endoballoon may be utilized.

Anterolateral Right Mini-thoracotomy Approach

In the right mini-thoracotomy, an anterolateral working port (4–6 cm) incision is made along the infra-mammary crease lateral to the nipple and through the right fourth ICS. The procedure is performed under direct visualization or with the aid of an endoscopic camera and long-shafted instruments are employed. A fixed left atrial blade retractor is introduced into the right side of the chest through the working port and connected to a 2-mm shaft penetrating the chest wall in the fourth ICS, just lateral to the right internal thoracic artery. Cardiopulmonary bypass is initiated using right femoral artery and vein cannulation. The Endoballoon or transthoracic clamp is used to occlude aorta.

Mitral Valve Repair Techniques

Triangular Resection

This technique is ideal for patients with posterior leaflet prolapse. The normal chordae on either side of the prolapsing portion are identified to determine the extent of resection. A triangular-shaped segment of tissue is excised (Fig. 41.1). Running 4-0 polypropylene suture with or without a ventricularization technique [17] is used to close the defect in the leaflet.

Quadrangular Resection with Sliding Repair

A quadrangular resection of the posterior leaflet is employed for management of extensive, redundant posterior leaflet prolapse. The prolapsing, excessively tall segment of posterior leaflet is excised and then the remaining portions of posterior leaflet are detached from the annulus and advanced centrally, "sliding" them over, to meet. The leaflet base is reattached to the annulus with running 4-0 polypropylene and the leaflet edges are reapproximated (Fig. 41.2).

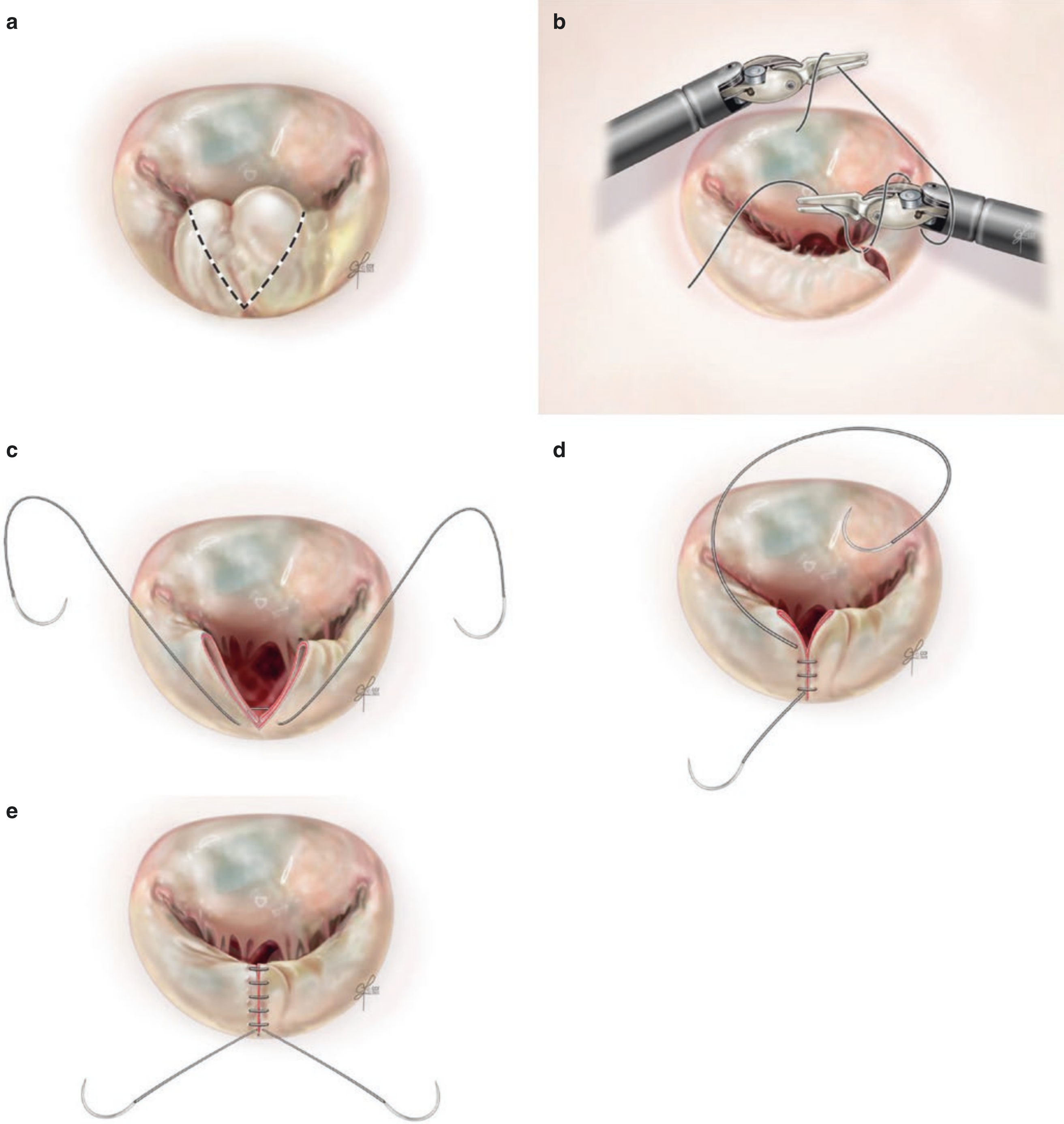
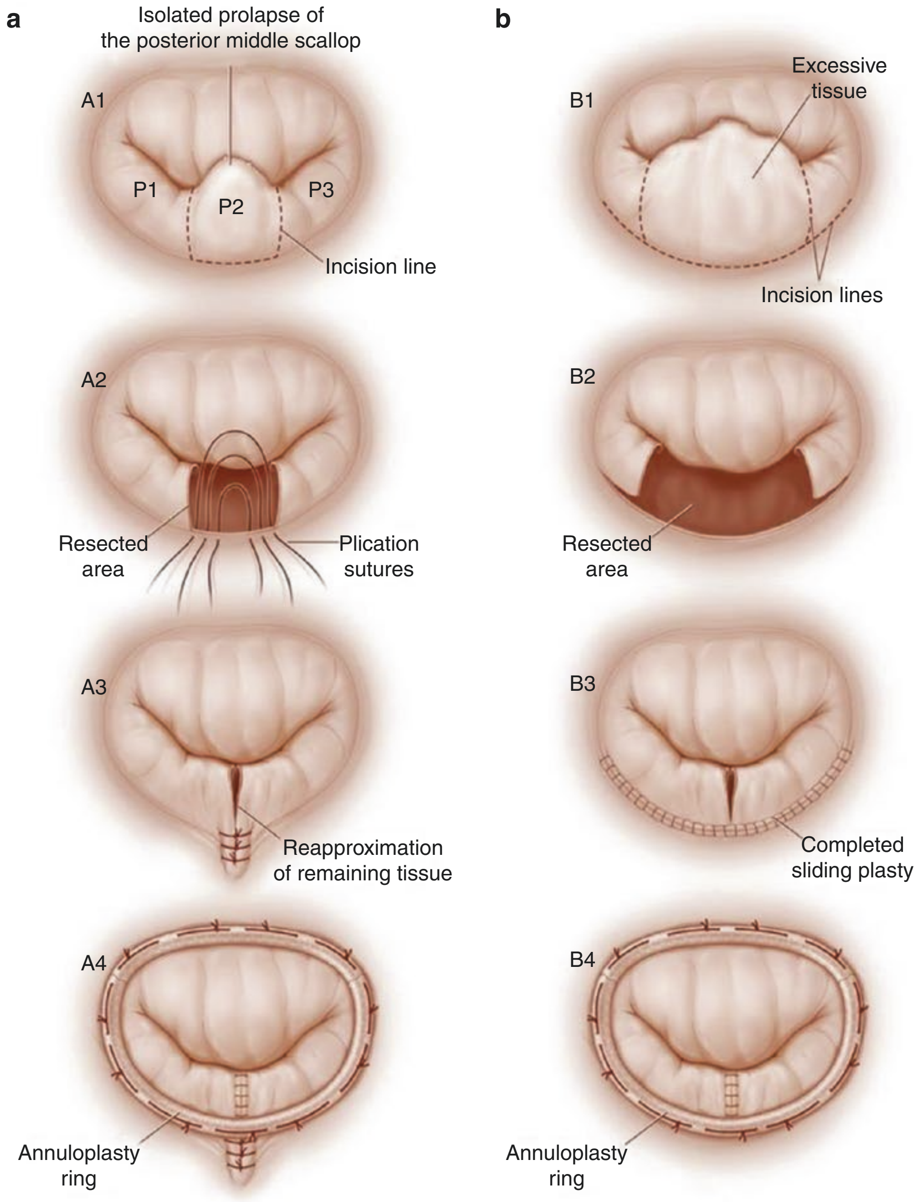


Fig. 41.1 (**a**–**e**) Triangular resection and repair of P2 prolapse

Neochordae Implantation

Polytetrafluoroethylene (PTFE) neochordae placement is facilitated by the robotic approach and is particularly useful for treatment of anterior leaflet prolapse. The neochordae are created using 5-0 PTFE suture. One arm of the suture is passed twice through the fibrous tip of the papillary muscle, then twice through the free edge of the corresponding prolapsing segment. The second suture arm is then passed twice through the free edge of the prolapsing segment. The length of the chordae is adjusted based on (1) the height of the nearest normal segment of the leaflet, (2) shorter than elongated chords, and (3) in a position which puts edge of mitral valve leaflet at the level of mitral annulus. The suture is tied on the atrial side of the mitral valve leaflet (Fig. 41.3).

Fig. 41.2 (**a**, **b**) Quadrangular resection with sliding plasty

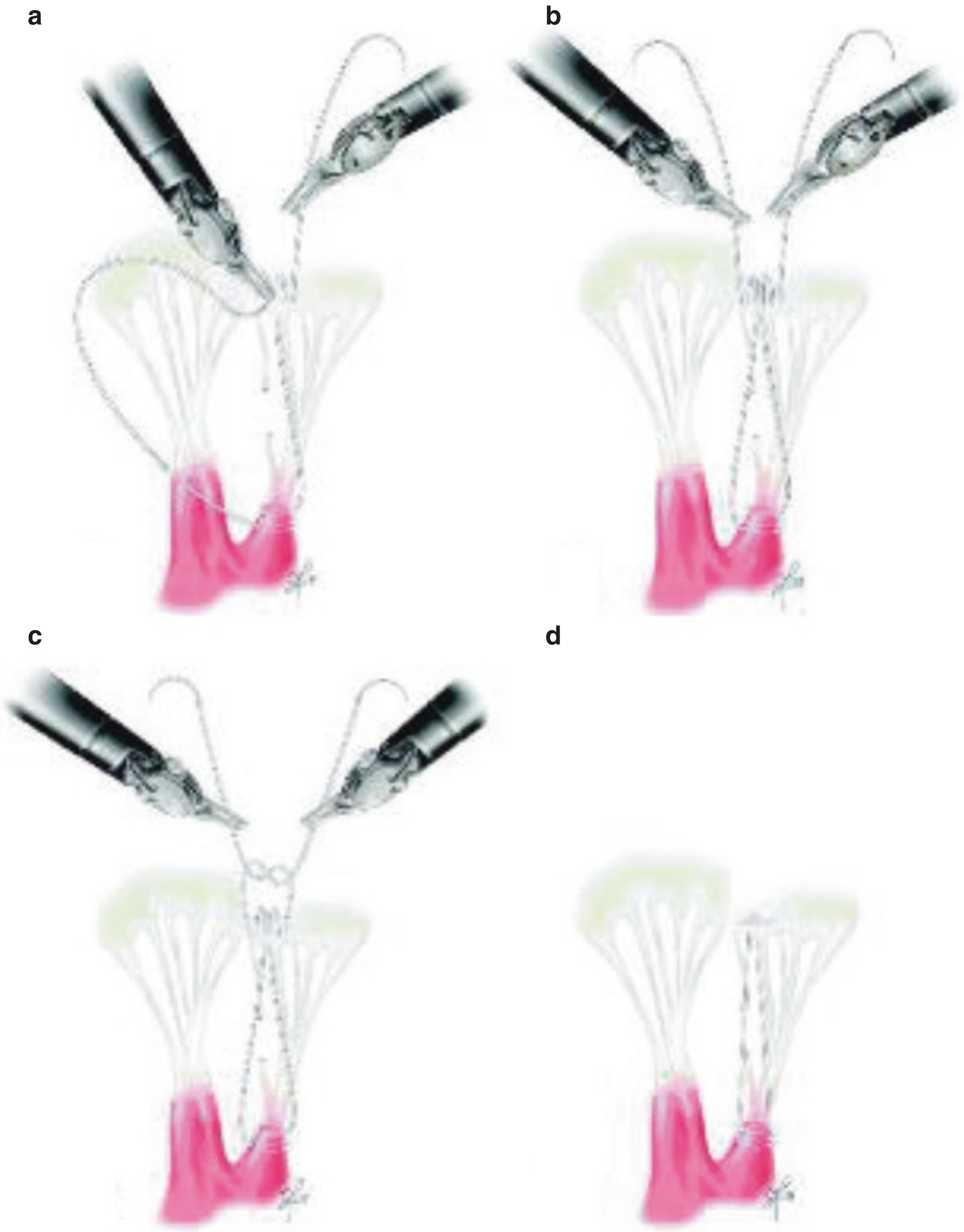

a
Isolated prolapse of the posterior middle scallop
A1
P1
P2
P3
Incision line
A2
Resected area
Plication sutures
A3
Reapproximation of remaining tissue
A4
Annuloplasty ring
b
Excessive tissue
B1
Incision lines
B2
Resected area
B3
Completed sliding plasty
B4
Annuloplasty ring

Annuloplasty

All repairs are completed using annuloplasty band. In minimally invasive approach, a flexible, standard-length annuloplasty band (63 or 65 mm) is used. The band is first secured at the right (medial) trigone and additional sutures are placed from the medial to the lateral part of the annulus using either running [18] or interrupted technique.

For the interrupted suture technique, 2-0 braided polyester sutures are used to secure the annuloplasty ring in standard fashion (Fig. 41.4). For the running suture technique, three 2-0 braided polyester sutures (Ticron, Covidien, MA) are used to secure the annuloplasty ring as follows. The first suture is tied down between the right trigone and the ring and run clockwise to the midportion of the ring. The second suture is started at this point with a single interrupted stitch and tied to the first suture. The remainder of the second suture is then run clockwise to the left trigone. The third suture (9 cm in length) is passed through the ring, through the left trigone, and then back through the ring. This third suture is tied down, and the tail is used to secure the second suture (Fig. 41.5).

Fig. 41.3 (**a**–**d**) Neochordae implantation



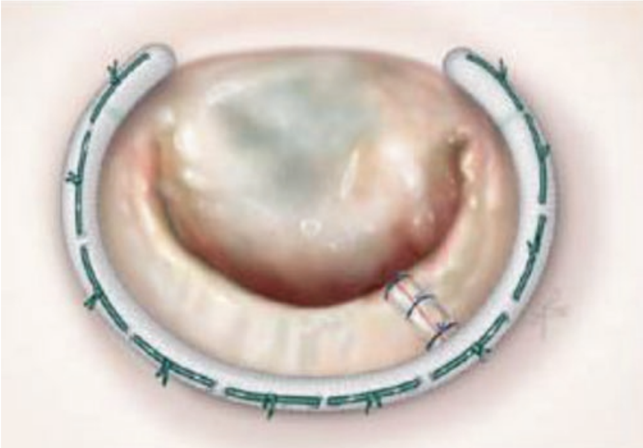


Fig. 41.4 Annuloplasty ring secured in standard fashion using interrupted suture technique

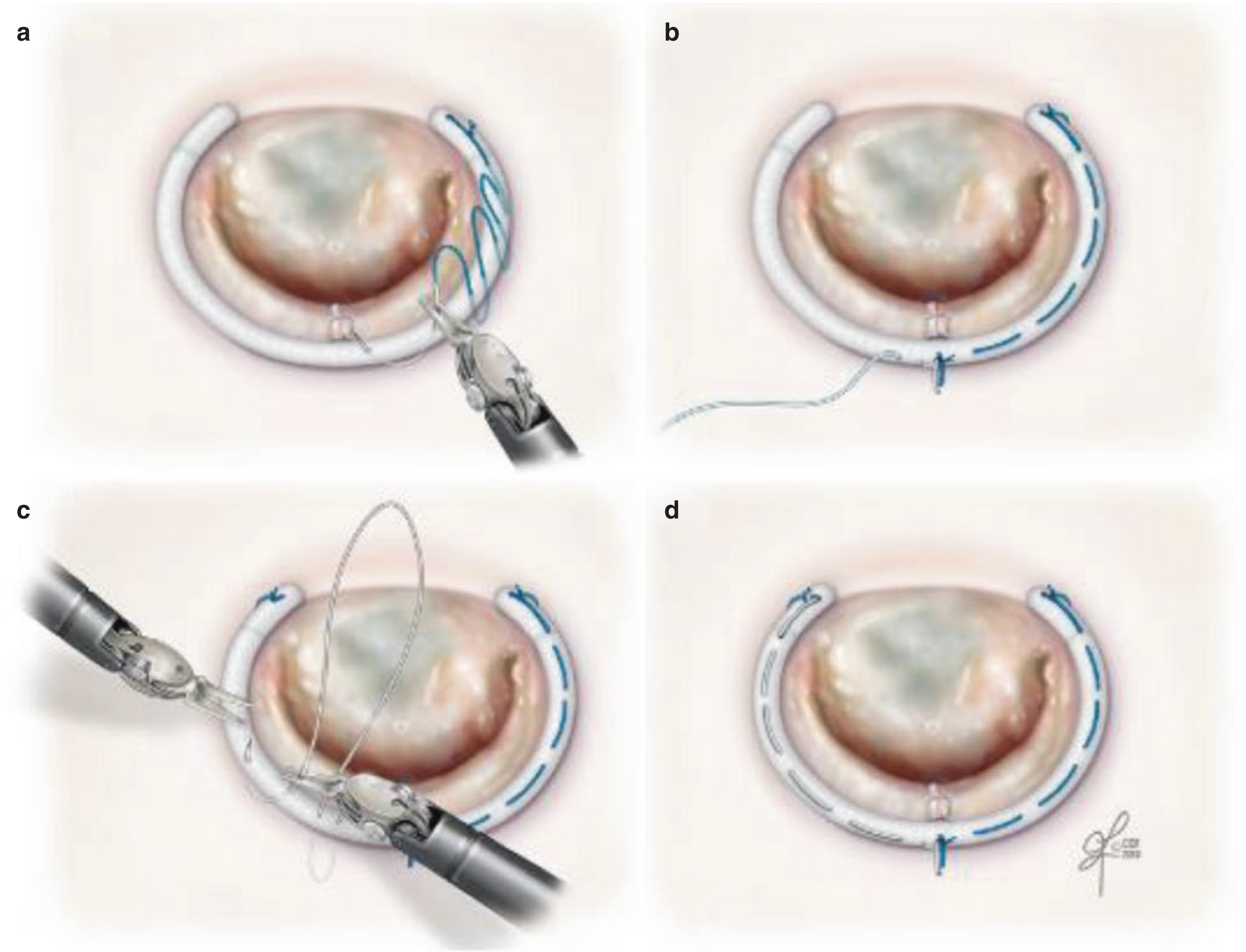


Fig. 41.5 (**a**–**d**) The running suture technique for securing the annuloplasty ring

Assessment of Repair

All repairs are assessed using saline insufflation to fill and pressurize the left ventricle before closure, de-airing, and cross-clamp removal. Integrity of the repair (≤+1 residual MR) and adequacy of de-airing should be confirmed with the patient off cardiopulmonary bypass before decannulation. Once the heart is beating (and preliminary evaluation of the repair by TEE is satisfactory), the antegrade cardioplegia catheter is removed from the aorta and the puncture site is closed.

The patient is then separated from cardiopulmonary bypass and the repair is evaluated by TEE. In minimally invasive approaches, the cannulas are removed while protamine is administered, the purse-string in the femoral vein is tied, and the femoral arteriotomy is repaired primarily. After protamine is administered, the right lung is deflated and the camera is reintroduced into the chest to examine the aortic cardioplegia site, as well as all port sites to ensure good hemostasis. All patients undergo TTE before discharge from hospital. It is our practice to recommend lifelong annual echocardiographic surveillance after mitral valve repair [16, 19–21].

Published Outcomes

Previous studies have demonstrated improved long-term survival for mitral valve repair compared with mitral valve replacement [4, 22, 23]. Repair is not associated with a survival benefit in the group of patients having extremely complex degenerative disease [19]. This subset of patients is typically older and has higher numbers of symptoms and comorbidities, and severe annular calcification [19].

The common goal of all minimally invasive mitral valve repairs is maintaining the same indications for mitral valve repair, upholding the technical and safety standards of sternotomy, and successful elimination of significant MR [24]. Safety and effectiveness of minimally invasive approaches have been facilitated by modifications in perfusion technology, intraoperative TEE, and novel repair techniques [6, 25, 26].

Several studies have documented the benefits of mini-thoracotomy mitral valve repair including faster extubation [27, 28], less postoperative pain [24, 29], bleeding, and transfusion [30], better cosmetic results, and shorter duration of intensive care unit and hospital stay [26] while hospital cost and long-term survival and durability of repair were similar to the sternotomy approach [31–33]. Furthermore, although cross-clamp and operative times are longer in some studies compared to conventional median sternotomy, there has been no compromise in operative safety and efficacy [34]. The collective results of robotic mitral valve repair performed by experienced groups include a hospital mortality rate of less than <0.9%, stroke rate of 0.6–1.7%, re-exploration for bleeding of <2.2–4.7%, and rare chest wall infections [35–40]. Furthermore, the incidence of iatrogenic aortic dissection, phrenic nerve palsy, and groin infections have all decreased to near 0% [40].

Conclusion

Mitral valve surgery has evolved over four decades from one based on the principles of prosthetic replacement to a subspecialty with a foundation based on the principles of repair. Mitral valve repair can be performed through complete sternotomy or minimally invasive approaches including partial upper sternotomy, right mini anterolateral thoracotomy and robotically assisted right thoracic approach. Minimally invasive approaches offer comparable quality of mitral valve repair without compromising safety. Adoption of simple and reproducible mitral valve repair techniques is of paramount importance to ensure that repair of all degenerative valves can be achieved with good mid- to long-term durability, regardless of valve morphology, patient age or comorbidities.

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42

Mitral Valve Repair in Rheumatic Mitral Disease

Taweesak Chotivatanapong

High Yield Facts

- Rheumatic heart disease is the most severe sequela of rheumatic fever and occurs in approximately 30% of patients with rheumatic fever.
- Rheumatic heart disease presents with varying degrees of pancarditis and associated valve dysfunction.
- Rheumatic heart disease is the leading cause of mitral valve disease in the developing world.
- Involvement of the mitral leaflets can cause mitral regurgitation or stenosis and eventually can lead to heart failure.
- In developing countries, mitral valve replacement is usually preferred in cases of rheumatic disease.
- Surgical repair is an acceptable way of converting a diseased valve to a functional valve, and it improves postoperative morbidity and survival.
- Although mitral repair is successful in up to 95% of patients with degenerative valves, repair procedures are feasible in only about 75% of patients with rheumatic valve disease.
- This difference is attributable to the varying degrees of inflammation on rheumatic valves, which can present with extensive fibrosis and calcification of the leaflet's free margin and chordal fusion. Moreover, occasional fibrosis and calcification of the papillary muscle, commissures, and annulus can hamper the success of valve repair.
- Various repair techniques—including commissurotomy, shaving of diseased leaflets, chordal division or transfer, neochordal replacement with GORE-TEX® or PTFE sutures, leaflet augmentation with pericardial patching, and splitting of papillary muscle—can be used in rheumatic valve repair.
- To enhance coaptation, an annuloplasty ring generally accompanies valve repair.

Introduction

Rheumatic heart disease remains a major problem in several parts of the world particularly in developing countries. Over the last five decades, mitral valve repair has stood the test of time for its advantages over valve replacement [1, 2]. However, in rheumatic mitral disease, the role of mitral valve repair is often questioned and uncertain. The problem is based on rheumatic mitral pathology which is a complex sequela of rheumatic inflammatory process. In addition to this, significant numbers of rheumatic patients come at a later stage when disease has progressed and caused much more damage to mitral complex. Common pathological changes include severe subvalvular and valvular thickening, valve tissue retraction and calcification. All of these changes become a real challenge for successful repair. Although mitral valve replacement is an attractive alternative operation, rheumatic heart disease commonly occurs in young, female patients from low socioeconomic background. They usually live in remote area with difficult access to the health care services and thus, mitral valve replacement is far from ideal for them.

In recent years, several innovative techniques and approaches have been introduced in surgical practice for improvement of success and durability of rheumatic mitral valve repair with encouraging results. The aim of this chapter is to review current state of the art as well as innovative techniques in repairing rheumatic mitral disease.

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Problem and Burden of Rheumatic Valve Disease

Rheumatic valve disease is the most common cause of acquired valvular heart disease in children and young adults worldwide. Rheumatic fever occurs in 3–4% of untreated group A streptococcal pharyngitis. The most serious sequela of rheumatic fever is rheumatic valvular heart disease that can occur in up to 50% of patients [3, 4]. In up to 50% of these patients, mitral valve can be affected and results in mitral regurgitation, mitral stenosis or both [5, 6]. Globally, rheumatic heart disease affects 33 million people same as human immunodeficiency virus [7]. It is well established that the effective treatment for symptomatic rheumatic valve disease is open heart surgery. However, it is woefully evident that lifesaving cardiac surgery is absent in many endemic areas. Although prevention measures are important to eradicate rheumatic heart disease strategically, but evidence of slow inroads that prevention has made in the past 15 years [8], implies that surgery will remain an integral part of treatment of rheumatic heart disease for several generations.

Mitral Valve Complex: Structure and Dynamics

Mitral valve comprises of four leaflets, anterior, posterior and two small commissural leaflets. The anterior leaflet is long and attaches to about one third of annulus anteriorly. It guides blood flow during diastole toward apex. The posterior leaflet is a strip of valve tissue attaching to about 2/3 of annular diameter. This anatomic character plays an important role during diastole to optimize blood flow from left atrium to left ventricle (LV). The leaflets must be pliable and move freely without obstruction to maximize normal diastolic flow through the ellipsoid mitral opening.

The commissural leaflets although small are integral for normal mitral dynamics. These move perpendicularly in relation to anterior and posterior leaflets. The chordal insertion often comes from a single papillary muscle as a fan-shaped chordal insertion. This is an important landmark to identify commissure which is often obscured in rheumatic mitral disease. With their anatomic character, commissural leaflets allow mitral valve to open maximally and close tightly with least stressful tension (Fig. 42.1).

Subvalvular apparatus is another most commonly affected area in rheumatic mitral disease involving chordal and papillary muscle structures. The crucial role of subvalvular apparatus is to provide active opening of mitral orifice, optimal diastolic blood flow and a secured systolic coaptation. To achieve these goals, mobility of leaflets must be normal, type I, brought about by normal primary chords. Stabilization of leaflet during systolic phase is taken care of by strong secondary chords. The integrated dynamic motion of papillary muscle and LV plays vital part in normal mitral dynamics, namely, active opening of mitral valve, maximal diastolic flow, changes in LV geometry to facilitate leaflet closure with good coaptation which is the ultimate goal of long term durability.

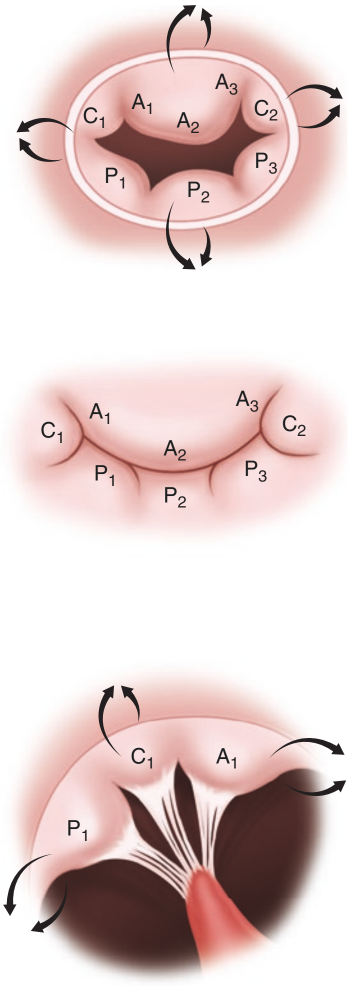

Fig. 42.1 Structure of normal mitral valve. *AML* anterior mitral leaflet, *PML* posterior mitral leaflet

Mitral annulus is the last but very important part to mention of mitral complex. It is the frame work for all mitral dynamics mentioned above. It is not planar but three dimensional and dynamic structure. The changes in size and shape are very delicate for optimal opening and closing of mitral valve, reduction of stress upon mitral apparatus and optimized movement of left ventricular outflow tract for unimpeded cardiac output.

Rheumatic Mitral Valve Repair: Current Approaches and Strategy

Mitral valve repair in rheumatic heart disease is based on thorough understanding of mitral valve complex and its dynamics. The complex comprises of at least six important components namely, left atrium, annulus, leaflets, chords, papillary muscles and left ventricle. These components work synchronously to respond to a wide range of physiologic demands of body in the most effective way. Rheumatic valve disease affects every part of mitral valve complex. It causes primary lesion to the affected part and results in dysfunction. This dysfunction further aggravates secondary lesion and so on. Understanding of this vicious cycle is mandatory for current approaches and repairing strategy of rheumatic mitral valve. To achieve an optimal mitral valve repair, surgeon must aim to do a holistic repair to restore normal physiologic function of each component of the complex as much as possible to allow mitral valve to function as closest to the normal natural state. Another important approach in contemporary era of mitral valve repair which has become a "must" routine is the use of intraoperative transesophageal echocardiography. This approach has greatly enhanced understanding and success of mitral valve repair. It should be included as an integral part of repair protocol in every specialized mitral valve repair center.

The principle of mitral valve repair is the same whether for rheumatic or non-rheumatic valve disease. However, the valve pathology in rheumatic disease is unique and significantly different from degenerative mitral valve disease. Most degenerative valve patients have excessive tissue with type II movement associated with thin, friable chords and dilated annulus. On the other hand, in rheumatic valve patients, tissues are retracted and shrunken while chords are thickened and either shortened or elongated. Annulus is quite often deformed and fibrosed. All of these unique pathologies mandate different approach and technique despite the fact that they are based on the same mitral valve repair principle, i.e., restoration of type I leaflet movement, good coaptation and remodeling of annulus with appropriate mitral annuloplasty. The current approach of mitral valve repair for each component of mitral complex can be elaborated as following.

Commissure

Commissural fusion is a common lesion even in patients with rheumatic mitral regurgitation. Commissurotomy is needed for correct assessment of leaflet motion. However, it is not uncommon that the commissural line is obscured by rheumatic process. A practical tip to help visualization is by pulling the mid-portion of anterior leaflet downward. This exposes two dimples of both trigones, a stable landmark. Few millimeters below trigone is the position to start commissurotomy by sharp incision toward the central mitral orifice. Care is taken to maintain a distance of 3–5 mm from the annulus to avoid mitral regurgitation. Meticulous chordal splitting and papillotomy to restore fan-shaped chordal insertion is helpful for normal commissural movement which is important for diastolic and systolic dynamics.

Mitral Leaflets

The most common leaflet problems in rheumatic mitral disease are thickening, retraction and calcification. All of these are consequences of rheumatic inflammatory process. They impair mobility and pliability of mitral leaflets and must be corrected with appropriate measures. Thinning of mitral leaflets can be done by peeling technique [9–11]. The technique improves pliability, expandability and length of the leaflet. Calcification can be partial or full thickness. Partial thickness calcification can be managed by combination of peeling technique and sharp resection at rough zone. Full thickness calcification usually needs complete excision and tissue repair with appropriate substitute e.g., autologous or bovine pericardium. This approach corrects quality, quantity as well as geometry of mitral leaflets which are essential for normal mitral valve function.

Chordae and Papillary Muscles

Subvalvular pathology is most challenging in rheumatic mitral repair. The chords usually are thickened, shortened or elongated, fused or calcified. In some conditions, the shortening of chords can be so severe that the head of papillary muscle is next to the leaflet. All of these changes interfere with normal function of mitral valve and result in type II or type III leaflet motion. Usually, these pathologic changes can be corrected by techniques advocated by Carpentier [1]. Chordal repair techniques vary from using native chordal transfer or neochordal replacement if good native chord is unavailable. Excellent long term results of synthetic neochordal replacement have been confirmed by several studies [12–15].

Chordal fusion is usually associated with shortened chords. Chordal splitting, papillotomy and fenestration usually in combination can solve this problem. Combined use of fenestration and papillotomy can improve effective chordal length and provide additional route of flow through fenestrated channel during diastole. With this approach, surgeon can achieve better diastolic function and good chordal repair with less need of synthetic materials.

Annulus

Annular involvement in rheumatic mitral valve is often complex. It may be thickened and deformed or both. Annular remodeling with prosthetic ring has become an integral part of mitral valve repair and provides better long term outcomes compared to those without ring. Annular dynamics has been shown to be related to type of ring, with flexible ring resulting in better LV function. However, for many of patients, the mitral annulus is already fibrosed, immobile and deformed.

Obviously, the primary concern is to correct deformity and restore normal physiologic frame work for normal mitral function. Complete rigid ring or semi-rigid ring provides better tool for this purpose. Use of prosthetic partial or pericardial band is infrequent in rheumatic mitral repair. Role of biodegradable ring, although attractive in children, is uncertain for mitral valve repair in rheumatic clinical setting.

Associated Problems

Tricuspid Regurgitation

One of the most common associated problems with mitral valve disease is functional tricuspid regurgitation. Management of this problem is still debatable between "leave it alone" or "repair as indicated" approach. Current evidence confirms an increase in late morbidity and mortality for "leave it alone" strategy compared to repair strategy. Dreyfus [16] is of the view that the term "functional" is a misconception. The tricuspid becomes pathologic once it dilates to a certain degree and will not recoil back spontaneously unless surgical correction with tricuspid annuloplasty is done. The best indicator to do tricuspid valve repair is the size of annulus rather than the degree of regurgitation. Dreyfus advocated annular diameter of 7 cm measured under cardioplegia in an arrested heart as a cut-off point to do tricuspid valve repair. Others have proposed an annular diameter of 4 cm measured by echocardiography. The question of whether tricuspid annuloplasty should be carried out with or without prosthetic ring is another debatable issue. Recent evidence in the form of studies with long-term follow-up [17–19] has shown that tricuspid annuloplasty with a prosthetic ring is associated with better long term outcome compared to those without ring.

Associated Aortic Valve Disease

Aortic valve repair has gained more attention recently with encouraging results by several studies [20, 21], however, its role in rheumatic valve disease is still doubtful and often pessimistic. Choice of surgical treatment for rheumatic patients with mitral valve disease and associated aortic valve problem is also a subject of debate whether to do mitral valve repair plus aortic valve replacement or double valve replacement. Gillinov et al. [21] have reported better long term results at 15 years in all subset of patients (rheumatic including severe mitral stenosis and non-rheumatic patients) with mitral valve repair and aortic valve replacement. Freedom from valve replacement in rheumatic mitral valve repair group was 75% at 15 years. It was advocated that mitral valve repair in this clinical setting is feasible and improves long term survival especially for the rheumatic patients who benefit most from survival advantages based on the evidence of this study. Ho et al. [22] reported results in a study of 609 rheumatic patients who underwent aortic valve replacement with either mitral valve repair or replacement. At 9 years, the mitral valve repair group had better long term survival and freedom from major bleeding compared to replacement group. Freedom from other valve related complications and mitral valve re-operation was comparable between both groups. This confirms the durability and reproducibility of mitral valve repair approach in this situation. It is thus advocated that mitral valve repair approach whenever it is possible should be a preferred operation in double valve disease involving aortic and mitral valves.

Valvular Atrial Fibrillation

Atrial fibrillation is a common associated finding in rheumatic mitral valve disease especially with long history of involvement and enlarged left atrium. Atrial fibrillation increases the risk of late cardiac event and stroke [23]. Early surgical treatment for atrial fibrillation was proposed by Cox [23] that included several classical "cut and sew" incisions. This complex operation carried several potential complications mainly bleeding, heart block or sinus arrest. Advances in development of alternative energy sources e.g. radio-frequency or cryosurgery etc., made atrial fibrillation surgery acceptable, safe and effective [24–26]. Concomitant atrial fibrillation surgery appears justified to reduce risk of cardiac events and stroke. Evidence has shown superior results of atrial fibrillation surgery by using biatrial approach although with the potential risk of heart block. In patients with dilated left atrium, left atrial size reduction is recommended to improve conversion rate to sinus rhythm and restoration of left atrial function [27–29]. Several modifications of surgical techniques and ablation have been introduced. Surgeons must adopt their own preference based on safety and efficacy for each individual patient.

The Technique of Rheumatic Mitral Valve Repair

Exposure

This is one of the most important steps in mitral valve repair. Surgeon must be familiar with the exposure approach he is using and MUST spend time to obtain an excellent exposure of every segment of mitral valve (Fig. 42.2). There are many excellent incisions for optimal exposure of mitral valve. Our routine exposure is via a combined superior transseptal approach or modified Guiraudon incision [30].

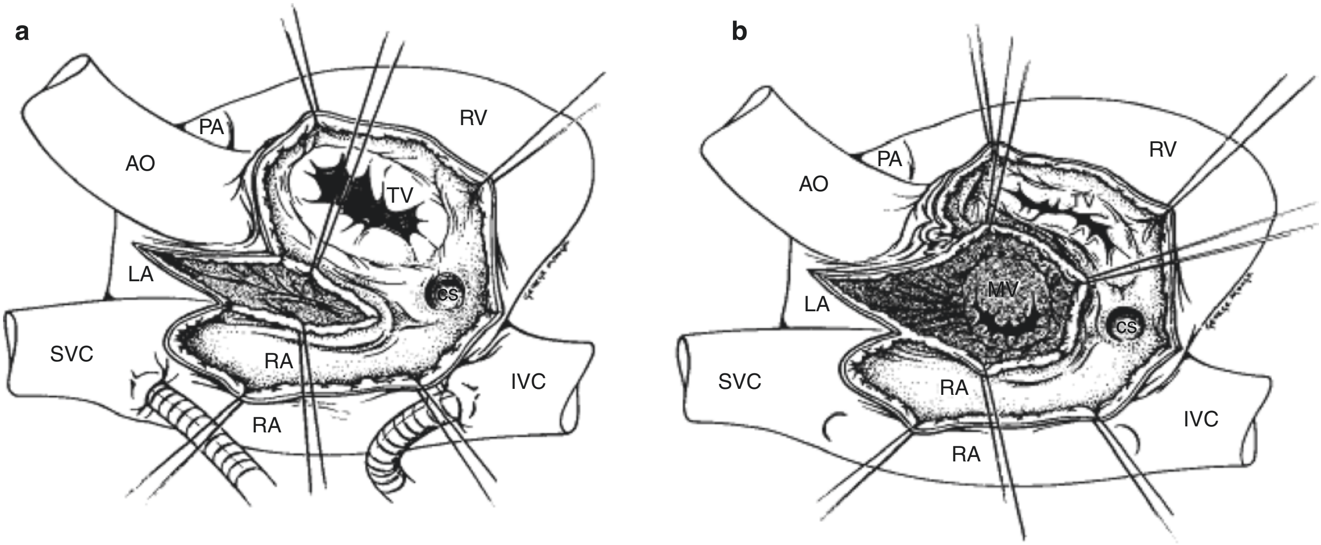

Fig. 42.2 Extended vertical transatrial septal approach to the mitral valve. (**a**) Semicircumferential right atriotomy widely opened to demonstrate the vertical septal incision extended into the left atrium. (**b**) The septal incision is splayed open by stay sutures to expose the mitral valve. (*AO* aorta; *IVC* inferior vena cava; *LA* left atrium; *MV* mitral valve; *PA* pulmonary artery; *RA* right atrium; *RV* right ventricle; *SVC* superior vena cava; *TV* tricuspid valve)

The steps to achieve exposure using the combined superior transseptal approach are as follows:

1. An incision is made at mid-part between right atrial (RA) appendage and superior vena cava.
2. Extension of incision toward left atrial (LA) roof above and RA below.
3. An incision is made at LA roof at least 1 cm away from aortic root to avoid injury to aortic valve and safe closure. An extension of incision to the inter-atrial septum is made at fossa ovalis close to the anterior rim away from posterior rim. This will preserve posterior pathway from SA node to AV node and avoid the risk of complete heart block.
4. Annular stitches using 2-0 polyester are placed from trigone to trigone posteriorly to facilitate optimal exposure.

Excellent exposure paves way for surgeon to undertake a systematic and complete valve analysis, another critical step for success of mitral valve repair (Fig. 42.3).

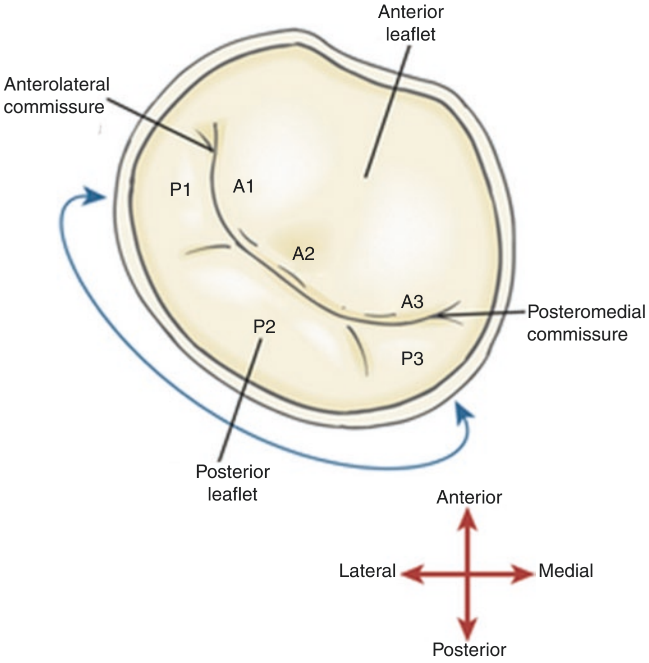

Fig. 42.3 Excellent exposure enables good analysis of all segments of mitral valve

Valve Analysis

Systematic valve analysis is important to delineate full details of valve pathology which is often complex. It is crucial for surgeon to obtain a correct and complete diagnosis of mitral valve pathology both in terms of localization and mechanism of mitral valve dysfunction. This is of paramount importance for a total correction of all pathology in every segment of mitral valve. We have found Carpentier's classification of mitral mobility into type I, II and III the most accurate and useful to understand mitral dysfunction and plan correct valve repair. For example, a "prolapse "anterior leaflet diagnosed from regurgitant jet of echocardiography, may actually be due to restrictive pathology of posterior leaflet from subvalvular restriction while the anterior is normal. Failure to recognize this problem may lead surgeon to address wrong side and failure of the repair.

Sequence of Rheumatic Mitral Repair

The sequence of rheumatic mitral repair is important. It ensures complete assessment and correction of mitral complex. These steps can be summarized as follows.

1. *Commissurotomy from commissure to commissure*

   This will allow surgeon to correct commissural structure and dynamics. Attention should focus on recreation of fan shape chordal appearance if possible. With good commissurotomy, surgeon can accurately assess the mobility of other segments correctly.
2. *Resection of restrictive or obstructive chords*

   One of the most common pathological lesions in rheumatic mitral valve is shortened and thickened chords that cause restrictive movement in systole and obstructive mobility during diastole. The goal is to mobilize leaflet movement back to type I. The target should be to focus on all pathological chords whether primary, secondary or tertiary. Not infrequently, type III motion ends up being type II motion, which can be corrected with appropriate chordal repair technique.
3. *Fenestration, papillotomy and chordal splitting*

   Subvalvular fusion is one of the common problems in rheumatic heart disease. The pathology not only causes restriction of mitral valve mobility but also interferes with the diastolic flow. This problem may be aggravated during situation of increased demand of cardiac output such as exercise and precipitate problem of exercise induced mitral stenosis etc. Chordal splitting along with papillotomy can be safely done down to 1/3 or even up to 1/2 of papillary muscle depending on the anatomy.
4. *Leaflet peeling*

   Mitral leaflets in rheumatic heart disease are often thick and retracted and thus disturb normal mitral dynamics. The aim of this technique is to restore the pliability of mitral leaflets. The technique has been introduced by Kumar [9]. Starting with blunt dissection at the hinge part of mitral leaflet closed to the annulus, one usually can find a cleavage plane (Fig. 42.4). With continued dissection, it can be thinned out from native leaflet down to rough zone and resected. It is now an integral part of rheumatic mitral valve repair tool kit that provides gratifying long term results (Fig. 42.5).
5. *Leaflet augmentation and reconstruction*

   Severe fibrosis, retraction and calcification are pathologies that complicate rheumatic mitral valve. Our current approach to eliminate these lesions is it to undertake peeling, thin it out or resect and do tissue repair using appropriate tissue substitute. Calcification of leaflet is a challenging lesion. It is usually the end result of long term fibrosis and retraction. It complicates repair and necessitates combined blunt and sharp dissection to eliminate this difficult problem. However, with accumulated experience, we can now achieve gratifying results of decalcification and restore normal leaflet function without need of tissue repair.

   However, when calcification becomes more severe and involves whole leaflet thickness, resection of calcification and tissue repair is required. Our preferred material is autologous pericardium treated with 0.65% glutaraldehyde solution for 10 min for leaflet reconstruction (Fig. 42.6) and polytetrafluoroethylene (PTFE) suture for chordal replacement (Fig. 42.7).
6. *Chordal repair*

   Chordal fusion and shortened chords are common in rheumatic mitral valve and cause mitral regurgitation,

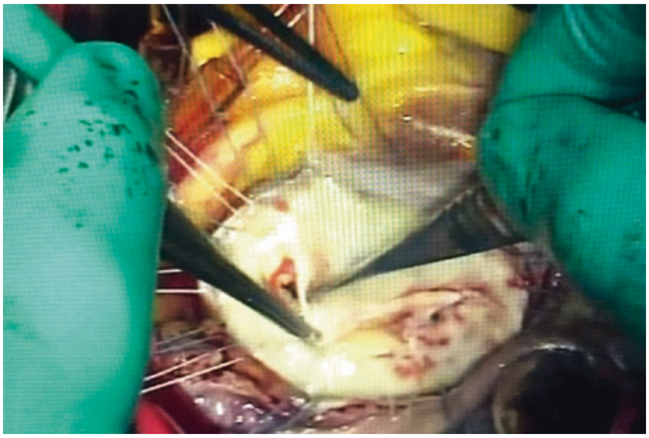

Fig. 42.4 Commencement of leaflet peeling

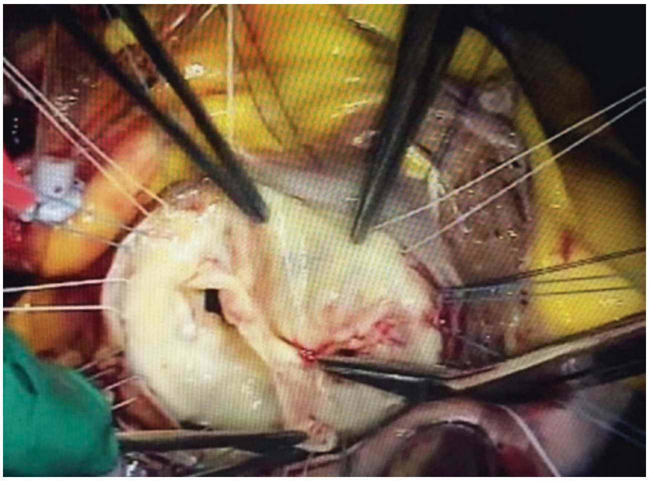

Fig. 42.5 Removal of leaflet peel

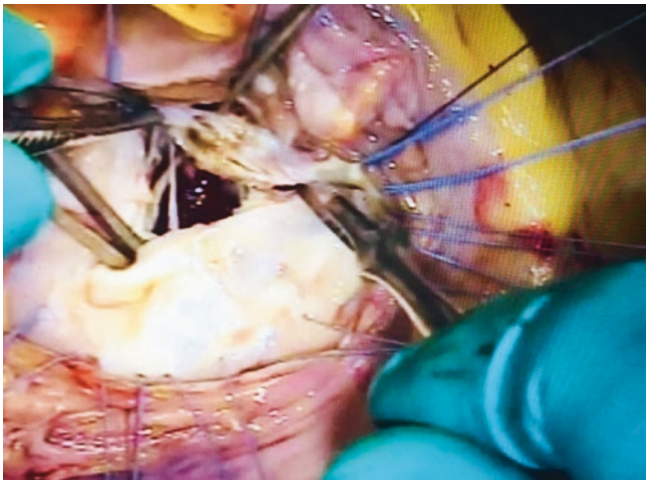

Fig. 42.6 Leaflet augmentation with glutaraldehyde-fixed autologous pericardial patch

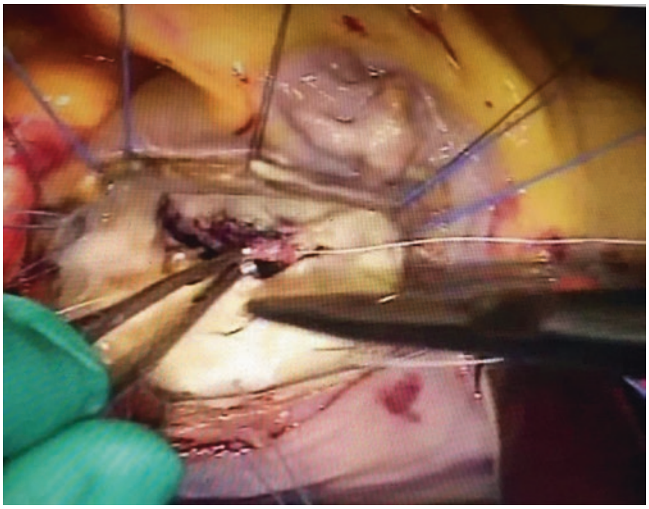

Fig. 42.7 Use of polytetrafluoroethylene (PTFE) suture for chordal replacement

stenosis or combined problems. Chordal repair to restore type I movement should be carried out by natural chord especially in young patients whenever possible. However, neochordal replacement is an effective alternative with proven good long term results [13, 31]. Recently, with use of fenestration, chordal splitting and papillotomy adequate chordal length can be achieved with good repair.

7. *Mitral annuloplasty*

   Mitral annuloplasty is an integral part of rheumatic mitral valve repair. The type of valve ring depends on pathology of mitral annulus. Usually, complete semi rigid or rigid ring is most effective to remodel mitral annulus and assure good long term durability of the repair. Choice of valve ring in a young patient especially when the annulus is small is still a debatable subject.

Table 42.1 Operations performed for patients with rheumatic mitral valve disease

Operation	Number
MV repair only	192
MV repair + TV repair	138
MV repair + MAZE	70
MV repair + TV repair + MAZE	60
MV repair + AVR + TV repair	23
MV repair + AVR	31
MV repair + CABG	10
MV repair + TV repair + ASD	2
MV repair + Other	8

ASD atrial septal defect, *AVR* aortic valve replacement, *CABG* coronary artery bypass grafting, *MV* mitral valve, *TV* tricuspid valve

Table 42.2 Echocardiographic & functional data for patients undergoing rheumatic mitral valve repair

Variable	Pre-op	Post-op
LVESD	35.49	33.88
LVEDD	52.15	48.01
EF	59.01	58.01
MR grade	2.58	0.23
MVA	1.74	2.27
NYHA FC	2.35	1.15

LVEDD left ventricular end-diastolic dimension, *LVESD* left ventricular end-systolic dimension, *EF* ejection fraction, *MR* mitral regurgitation, *MVA* mitral valve area, *NYHA FC* New York Heart Association functional class

Results

Based on our current approach of rheumatic mitral valve repair, a total of 534 patients underwent rheumatic mitral valve repair at Central Chest Institute of Thailand between January 2003 and December 2016. There were 352 females and 182 males with the average age of 46.79 years. Mean follow up was 41.9 months. The number of patients according to type of mitral problem in this group was 203, 195 and 136 for rheumatic MR, mixed MSMR and MS respectively. Details of operation and surgical techniques are shown in Table 42.1. There were 8 in-hospital deaths (1.4%). Eight patients died late of which 5 were cardiac related and 8 were non-cardiac in origin. Re-operation was required in 12 patients. Redo mitral valve replacement was done in 8 patients and repeat mitral valve repair in the other 4 without mortality. There were 57 readmissions with the main problems being congestive heart failure (21), pericardial effusion (20) and anticoagulation overdose (9). Six patients were readmitted with symptoms of moderate to severe regurgitation. One patient was readmitted with cerebrovascular symptoms that recovered with conservative treatment. The functional status of those successfully repaired patients improved substantially. Favorable mitral valve function was shown by postoperative echocardiography (Table 42.2). The improvement of echocardiographic findings in rheumatic

MS and rheumatic MR patients confirmed the effectiveness of mitral repair in this challenging group of patients.

Conclusion

Mitral valve repair for rheumatic mitral valve disease should be considered as an effective surgical treatment. It is feasible, safe and reproducible with acceptable good long term results. Although rheumatic mitral valve has a complex pathology and thus technically more demanding to repair, current techniques and many innovative approaches enable surgeons to have high rate of success with durable mitral valve repair. Despite concern of re-operation following repair, the long term advantages of repair offset the worry of repeat surgery.

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Native Valve Endocarditis

43

Kareem Bedeir and Basel Ramlawi

High Yield Facts

- The incidence of infective endocarditis has increased with a tendency towards more virulent organisms.
- Diagnosis is often not straight-forward, with a recent increase in culture-negative infective endocarditis.
- Indications of surgery include cardiogenic shock, para-annular extension, abscesses, fistulas, conduction abnormalities, persistently positive cultures or high embolic risk.
- Timing of surgery is of paramount importance for optimal outcomes. During optimization, close and vigilant monitoring is necessary with an understanding of early signs of decompensation and availability of urgent surgery.
- Surgical principles include eradication of infection and restoration of damaged cardiac structures. This often requires extensive atypical operations that necessitate good planning, sound surgical technique and a deep understanding of the surgical anatomy of the base of the heart.

Introduction

Despite advances in cardiovascular diagnostics and therapeutics, infective endocarditis (IE) remains a challenging disease with an overall mortality of up to 40% [1, 2]. Unfortunately, this mortality rate has not significantly changed over the last few decades [3, 4]. An abnormal valve, while more susceptible, is not required for endocardial seeding with infection, especially with the recent rise of incidence of IE caused by more virulent organisms like Staphylococcus aureus [5]. This has also led to IE with a more destructive pattern. Infective endocarditis of the aortic valve (AV) is more common than that of the mitral, due to a less densely fibrous annulus in the aortic position making it more susceptible to invasion. The mitral valve (MV) when affected has a higher risk of systemic embolization. Aortic, mitral and tricuspid IEs are rarely distinct processes, and a spectrum is appreciated with an understanding the anatomy.

Relevant Anatomy

The AV is at the center of the base of the heart with right (R), left (L) and non-coronary (non-C) cusps. It is intimately related circumferentially to various structures that are all jeopardized with extension of IE. Two fibrous trigones extend into the infra-annular plane, extending from almost the midpoints of the L and the non-C, and extend vertically a few millimeters towards the ventricular apex, to support the posteromedial and anterolateral commissures of the MV (right and left trigones, respectively). The intervening step-off between the two valve annuli and in between the trigones is the aortomitral curtain which suspends the anterior mitral leaflet (AML), and is crucial for the normal dynamic relationship between the two valves during the cardiac cycle. To the right of the right fibrous trigone, the membranous septum extends to a few millimeters anterior to the R/non-C commissure. This area is intimately related to the conduction system and various forms of conduction blocks occur with invasion of this area, which together with the right trigone are called the fibrous skeleton of the heart. Invasion into the membranous septum thus can connect the left ventricular outflow tract to the right sided chambers, either below or above the tricuspid valve (ventricular septal defect (VSD), or left ventricle (LV) to right atrium (RA) fistula, respectively). Between the membranous septum and to the left trigone, the

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aortic annulus is related to the muscular septum. Supra-annular extension, especially above the R/L commissure (towards the right ventricular outflow tract (RVOT) and pulmonary valve), or above the L/non-C commissure (towards the left atrial (LA) dome) can particularly perforate into the pericardium creating a potentially fatal cardiac tamponade. Understanding these intimate relationships is of utmost necessity for understanding complications, eradication of infection and for a technically sound reconstruction.

The Decision to Operate

Unless an immediate indication for surgery exists, a period of medical therapy and close monitoring should take place. Details of the diagnosis are beyond the scope of this chapter but are typically through echocardiography and bacterial isolation in blood. Broad spectrum intravenous antibacterial therapy is started and modified after bacterial identification. During that period, very strict and close monitoring is crucial. Indications for surgery in IE are dynamic and can occur at any time during the monitoring period. Failure to recognize delayed appearance of a surgical indication often leads to dismal outcomes that are neither justified nor accepted.

During the initial monitoring period, sepsis protocols should be adopted with special attention directed towards clinical examination, neurological examination, parameters of systemic sepsis and fever patterns, daily electrocardiograms, frequent echocardiograms, and surveillance blood culture after three days of effective antibacterial therapy. These are important early indicators of failing medical therapy or of an evolving surgical indication that should be urgently addressed.

Table 43.1 Indications of early surgery (before completion of full therapeutic course of antibiotics) [6, 7]

Class I	*Indicated* with valve dysfunction resulting in symptoms of HF.
	Indicated with left-sided IE caused by *Staphylococcal aureus*, fungal, or other highly resistant organisms.
	Indicated with IE complicated by heart block, annular or aortic abscess, or destructive penetrating lesions.
	Indicated with evidence of persistent infection as manifested by persistent bacteremia or fevers lasting longer than 5–7 days after onset of appropriate antimicrobial therapy.
Class IIa	*Reasonable* with recurrent emboli and persistent vegetations despite appropriate antibiotic therapy.
Class IIb	*May be considered* with NVE exhibiting mobile vegetations greater than 10 mm (with or without clinical evidence of embolic phenomenon).
	May be considered with an indication for surgery in a patient who has suffered a stroke but has no evidence of intracranial hemorrhage or extensive neurological damage.

All levels of evidence: B

HF heart failure, *IE* infective endocarditis, *NVE* native valve endocarditis

Indications for surgery are illustrated in Table 43.1 according to the 2014 American College of Cardiologist/American Heart Association (ACC/AHA) and the 2017 update guidelines [6, 7].

Congestive Heart Failure

Congestive heart failure (CHF) carries the worst outcomes regardless of approach to management [8, 9]. It is usually secondary to valvular regurgitation or fistula formation, leading to sudden volume overload. This can happen with leaflet perforation or destruction, erosion into a contiguous chamber, or in the mitral position chordal or papillary muscle rupture. In rare occasions, CHF can be caused by an obstructing vegetation. CHF is a class I indication for surgery [6]. Studies over multiple decades show clear survival benefits with surgery in IE with CHF compared to medical therapy (23% vs. 71%) [10–12]. With hemodynamic compromise, delay in surgery of more than 24 h is not acceptable. In more stable patients, CHF should be identified early with serial echocardiograms. Signs of impending CHF should be looked for. In these patients early, non-surgical management including antimicrobials and hemodynamic optimization with afterload reduction can be adopted, with strict monitoring and readiness for surgery with any deterioration. This can allow time for delayed surgery on a more stable, less acutely infected patient. Surgery is however almost always eventually required. It is important to differentiate hemodynamic compromise secondary to sepsis from that due to IE-related structural compromise. For the latter, surgery is urgently indicated. For the former, antibiotic and medical stabilization should be undertaken first, with surgery delayed until stable from a septic shock standpoint.

Para-annular Extension

Para-annular extension of infection is the most common complication, affecting almost 40% of NVE (100% of prosthetic valve endocarditis) [13]. This represents a class I indication for surgery, although the time frame is less defined. This is more common with Staphylococcal infections. Para-annular extension can lead to several complications including rupture of one chamber into another or into the pericardium, abscesses and conduction abnormalities and blocks. Suspicion of PAE with failure of resolution of inflammatory markers and/or persistent blood cultures after a period of appropriate antimicrobial therapy, is confirmed with daily electrocardiograms and serial echocardiograms documenting one of the above-mentioned complications.

Systemic Embolization

Systemic embolization occurs in 50% of patients with IE, with 30% of patients with IE developing a neurological event [14, 15]. Unfortunately, cerebral embolization comprises 60% of all embolic events, however no vascular bed is immune [16, 17]. Infected emboli lead to pathologies related to both ischemia as well as sepsis, including infarcts, mycotic aneurysms and abscesses. During the monitoring period, it is prudent to identify patients at high risk of embolization since these patients may benefit from early surgery. These include left sided endocarditis, especially those of the MV particularly the AML, large vegetations (>10–15 mm), moderate to severely mobile vegetations, enlarging vegetation despite antimicrobial therapy, first 2 weeks of therapy, as well as IE caused by certain pathogens (Staphylococcus aureus and fungus) [14, 18–21]. A randomized controlled trial compared antibiotic therapy to surgery within 48 h for patients having vegetations >10 mm, and no other immediate indications for surgery. There was a significant superiority for early surgery in composite outcomes of all-cause mortality and systemic embolization [22].

Computerized tomography (CT) of the brain is warranted with any suspicion of cerebral embolization. The previous teaching of waiting 2 weeks prior to surgery with embolic strokes is currently unfounded, with accumulating evidence that early surgery prevents further embolism and does not lead to hemorrhagic conversions [18, 23]. In case of hemorrhagic strokes, a wait time is recommended, however the exact time is not clear. A CT angiogram is indicated to diagnose any unruptured mycotic aneurysms that can be addressed by neurosurgery in prevention of further cerebral hemorrhage. The timing of surgery in this situation is a balance between the size of the bleed together with the urgency and complexity of the anticipated operation. Splenic or other visceral abscesses should be suspected with evidence of persistent sepsis despite appropriate antimicrobial therapy. A CT scan of the abdomen and pelvis is thus recommended prior to valve surgery in IE, unfortunately however, this does not always differentiate splenic infarcts from abscesses, so clinical correlation is required.

In general, *Staphylococcal*, *fungal*, *gram-negative as well prosthetic valve IE* are considered surgical diseases given the rare success of medical therapy in these categories. There should hence be a low threshold for surgery in these conditions.

General Surgical Principles in Endocarditis Surgery

Almost half of the patients with left-sided IE will require surgical intervention [24]. Surgical management of IE revolves around (1) complete eradication of the infected and necrotic tissue to control sepsis and, (2) restoration of damaged cardiac structures to avoid adverse hemodynamic effects. Achieving these two goals often requires quite complex and lengthy operations. It is important to understand however that these patients will tolerate a long complex procedure much better than tolerating residual infection secondary to inadequate debridement.

Prior to surgery for IE especially with risk factors for coronary artery disease, coronary anatomy and pathology should be addressed. Coronary catheterization can be time consuming and hazardous especially if crossing the aortic valve is attempted. We prefer coronary CT angiography in this instance. Two more advantages to the latter is that CT also gives a better anatomical appreciation for any potential grafts that need to be watched for during chest entry in patient with previous coronary bypasses, as well as identify severe aortic calcification that may alter cardiopulmonary bypass strategy when known ahead of time.

In the operating room, all intravascular lines should be replaced prior to incision. Endocarditis is usually addressed through a full sternotomy. Given the anticipated possibly prolonged operation, attention to conduct of bypass and rigorous myocardial protection is key towards surgical success. It is reasonable to consider femoral-femoral cardiopulmonary bypass (CPB) with revision surgeries, despite some evidence for elevated neurological events with retrograde perfusion in mitral surgery [25, 26]. In the case of aortocaval CPB, superior and inferior cava should be individually cannulated in anticipation of right atrial or septal involvement requiring exploration of the right-sided chambers. With suspicion of extensive PAE into the fibrous trigone, it is helpful to cannulate the superior vena cava as cephalad as possible, up to possible individual cannulation of the innominate veins to allow for possible superior vena caval transaction for better left atrial dome access and better surgical exposure. With debridement, multiple specimens should be obtained for microbiologic and pathologic examination. As a rule, sharp debridement is favored over curettage since a curette tends to spread the infection and may disrupt already organized underlying healing tissue. After debridement, our preference is to switch the instrument set, replace the draping towels and change surgical gloves, although there is insufficient data to support this practice.

Every effort should be made to avoid implanting a prosthetic valve, whether cadaver, xenografts or mechanical. Repair is more commonly possible in mitral IE than with aortic valve IE. This highlights the importance of optimal timing for intervention, since repair has a higher likelihood if surgery is undertaken early before extensive damage [27, 28].

Reconstruction

Thorough understanding of the anatomy and careful examination of the defect is crucial to understanding the extent of damage. A thorough assessment is key in identifying the correct surgical approach. IE starting around the aortic valve can become a technical challenge due to the central location of the valve, making invasion into other structure likely and necessitating reconstruction. Similarly, IE of the mitral valve can be technically challenging as well particularly when repair is perceived as a strategy to avoid replacement.

Mitral Valve

Repair is superior to replacement and should be the goal whenever possible. Reports of mitral repair in the setting of IE have varied largely based on patient population, organisms, extent of disease, techniques and experience. Rates of repair have ranged from 15% to 80%, being more likely in either healed or in early active IE [27–35]. This emphasizes the importance of early intervention when indicated. Repair is associated with improved survival, freedom from re-infection, decreased stroke rates and freedom from reoperation [29, 31, 32, 34, 36, 37]. Zegdi and colleagues report 91% freedom from reoperation and 92% freedom for more-than-trivial mitral regurgitation at 10 years, using standard Carpentier techniques [31]. Unfortunately, despite the superiority of repair, a recent large report showed less than 20% repair rate [35]. These rates are significantly lower than rates reported by high-volume centers, showing that real-world experience lags, and indicate an opportunity for improvement. If repair cannot be achieved, the choice between bioprosthetic versus mechanical valves should be based on patient-related factors similar to non-endocarditis patients. Short and long-term survivals as well as re-infection rates are similar with both valves [38–40]. Isolated mitral valve homografts are technically difficult and only limited experience and knowledge exist regarding their performance and long-term outcomes [41, 42].

Leaflets are addressed based on location of IE and extent of destruction. Stalked vegetations can be debrided without significant leaflet tissue loss. This may not result in a perforation, or a small one that can be repaired primarily. With extensive defects, patching is necessary. Patches are fashioned using bovine or autologous pericardium. With anterior leaflet defects, defects are more likely to be easily patched unless the defect is at the free edge. These are more challenging and might require chordal re-attachment. Posterior leaflet defects tend to require more techniques owing to the smaller leaflet area with longer area of attachment, necessitating triangular resection or quadrangular resection with sliding plasty or annular plication.

Loss of chordae requires reconstruction. Chordal reattachment can be achieved using chordal transfer from a nearby area of the same leaflet, or from a transposed leaflet. We prefer these techniques (autologous chordae) over neo-chords in an infected field whenever possible.

Annular debridement for periannular abscesses creates the most challenges. With significant atrioventricular (AV) discontinuity caused by debridement, lack of sound annular reconstruction can lead to catastrophic atrioventricular disruption. If the defect is small, figure-of-8 sutures can be used to close it. Atrial and ventricular bites should be taken separately and should evert the tissue harbouring the circumflex artery outwards away from next suture line for posterior leaflet or prosthetic valve attachment. If a larger defect is appreciated, the posterior annulus can be reconstructed by one of three methods: (1) Atrial sliding was described by Carpentier with excellent results for both posterior mitral annular calcification (MAC) or posterior annular IE [43]. The atrial wall is mobilized away from the annulus to obtain mobility to cover the annulus without much tension (atrium goes down, not the ventricle comes up). (2) Anterior leaflet transposition, although this was only reported with MAC [44]. This technique also commits the surgeon to replacement even if the valve was otherwise repairable. (3) Patching the annulus using bovine or autologous pericardium is the most widely used. It was pioneered by Tirone David and can be used for reconstructing both the anterior and posterior annuli as well as the aortomitral curtain [45]. The native leaflet as well as an annuloplasty ring can be attached to the patch, or alternatively a prosthetic valve can be mounted.

Aortic Valve and the Aortomitral Curtain

In contrast to MV IE, replacement is usually necessary for AV IE, with or without peri-annular reconstruction. Almost 15% of left sided IE affects both the aortic and mitral valves, with the intervening aortomitral curtain (AMC) being destroyed and requiring reconstruction [8]. All the options available for reconstruction are complex operations requiring extensive experience. Multiple options exist: (1) *Prosthetic valves* (mechanical or biological) are frequently used. The size of the defect dictates the extent of patching required, which then dictates whether autologous or bovine pericardium will be used. With reconstruction of fistulas or subannular defects, careful understanding of the anatomy of the conduction system and the fibrous skeleton of the heart is crucial. Key to reconstruction of the AMC is reconstruction of the fibrous trigones with enough vertical purchase, to step-off the MV and AV planes (Fig. 43.1). With significant supra-annular root destruction, (2) a *composite valved graft* can be used with coronary reimplantation, however prolonged anti-

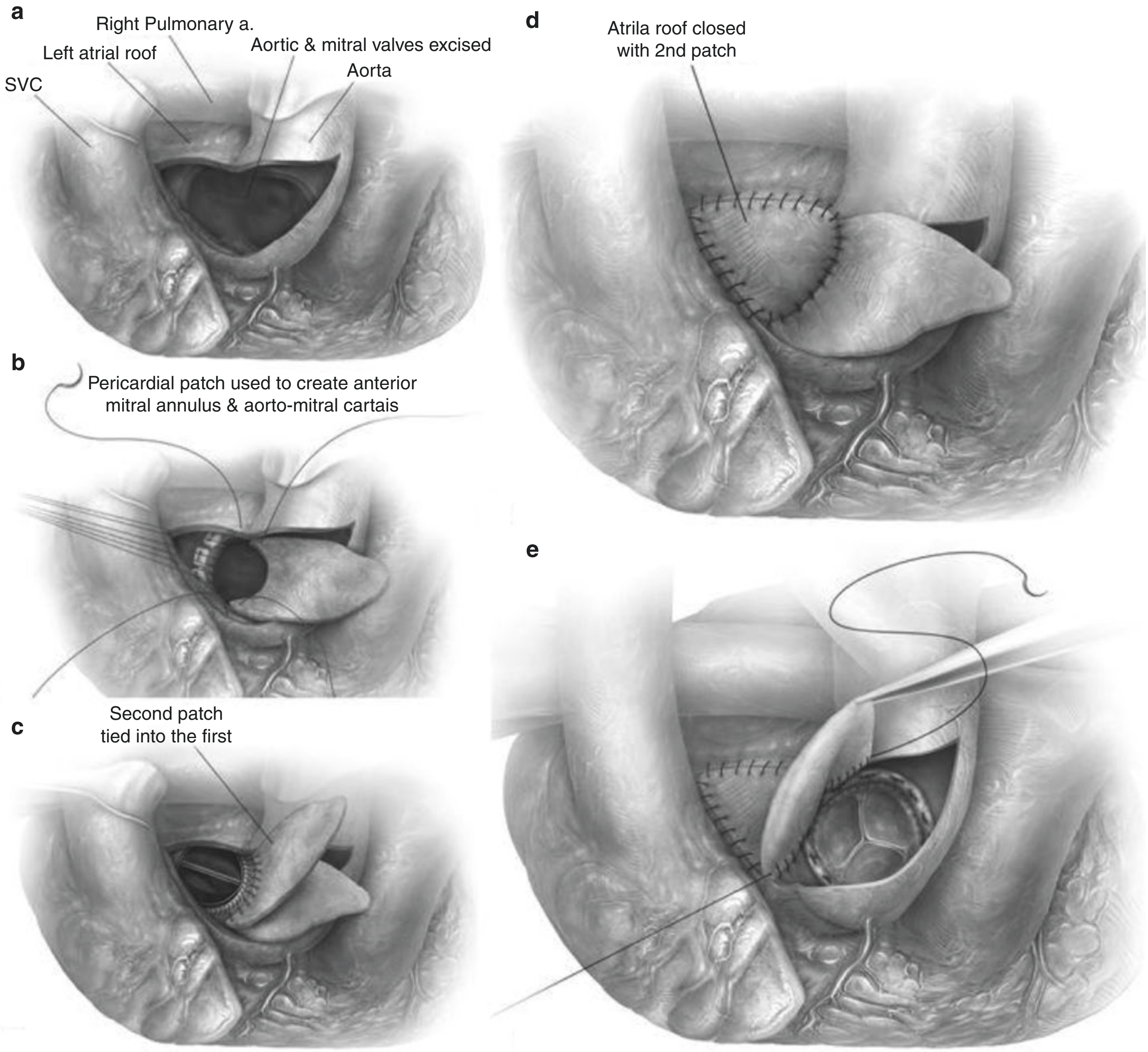
a
Right Pulmonary a.
Left atrial roof
Aortic & mitral valves excised
Aorta
SVC
b
Pericardial patch used to create anterior mitral annulus & aorto-mitral cartais
c
Second patch tied into the first
d
Atrila roof closed with 2nd patch
e

Fig. 43.1 (**a**–**e**) Double patch technique for endocarditis involving aortic and mitral valves and the aortomitral curtain. (With permission: Ramlawi B, Reardon M. Endocarditis with involvement of the aortomitral curtain. Op Tech Thorac Cardiovascular Surg, 2011;16:3:242–9)

biotic therapy will be required with such a graft. The preferred approach is the (3) *homograft technique*. Excellent outcomes have been reported [46–49]. The homograft can be used to replace the root, the AV, the muscular or membranous septa, the AMC and the AML, or can be trimmed as needed to suit the resultant defect (Fig. 43.2) . Homografts have the advantages of superior hemodynamics, do not require anticoagulation, better resistance to reinfection as well as available paravalvular tissue for reconstructing the root, the interventricular septum, the AMC or the AML. The downsides of homografts however are technical complexity compared to implantation of prosthetic valves and valved conduits, as well as subsequent calcification and degeneration requiring eventual reoperations which are significantly difficult technically. In younger patients this can be avoided by a (4) *pulmonary autograft (Ross operation)*, although this operation is not widely prevalent due to technical complexity and a long learning curve.

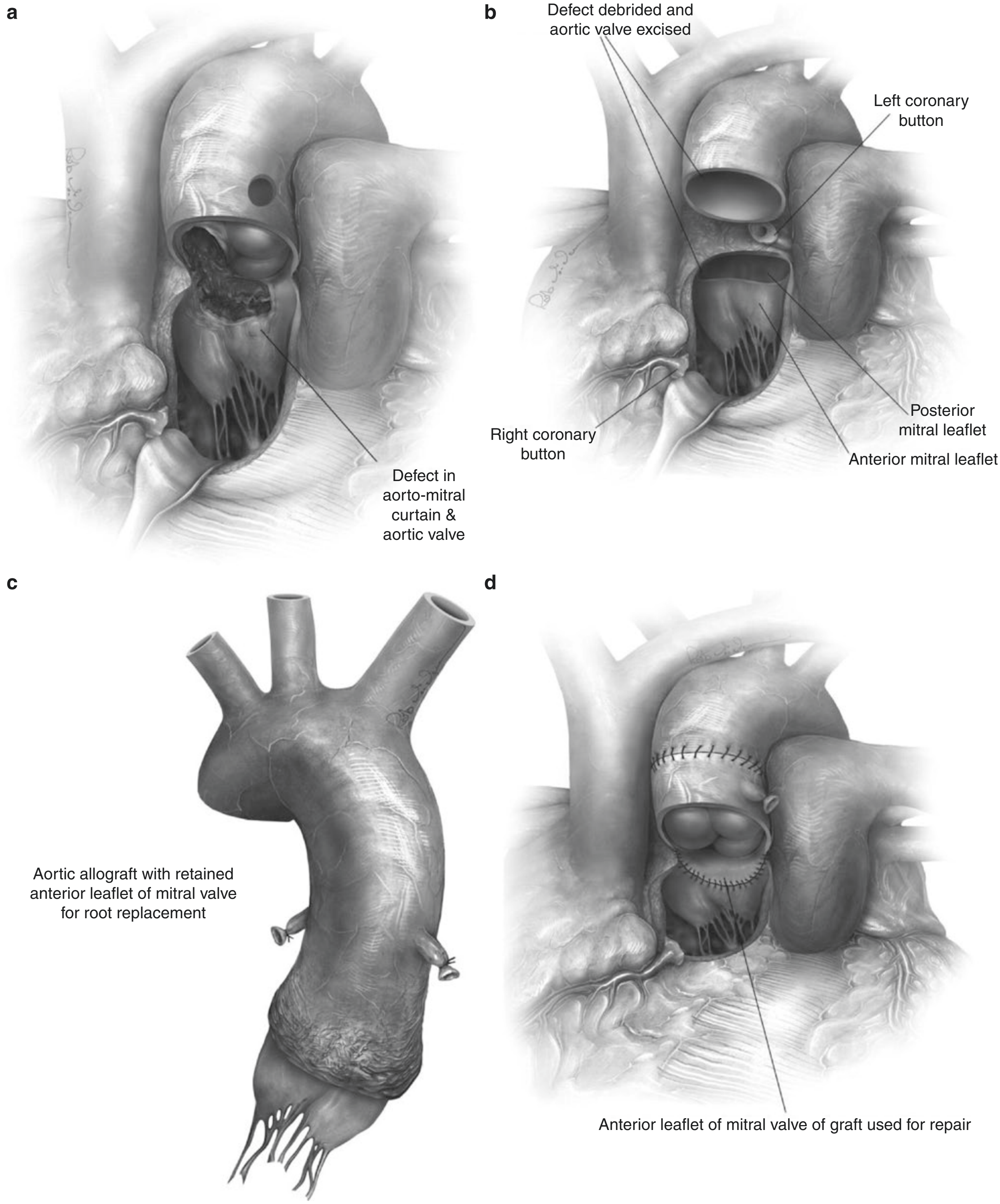
a
b
Defect debrided and aortic valve excised
Left coronary button
Defect in aorto-mitral curtain & aortic valve
Right coronary button
Posterior mitral leaflet
Anterior mitral leaflet
c
d
Aortic allograft with retained anterior leaflet of mitral valve for root replacement
Anterior leaflet of mitral valve of graft used for repair

Fig. 43.2 (**a**–**d**) Homograft technique for endocarditis involving aortic and mitral valves and the aortomitral curtain. (With permission: Ramlawi B, Reardon M. Endocarditis with involvement of the aortomitral curtain. Op Tech Thorac Cardiovascular Surg, 2011;16:3:242–9)

Conclusion

Infective endocarditis is a serious disease with significant mortality even when appropriately treated. Success in management revolves around a correct diagnosis, close monitoring, timing of intervention and sound implementation of the appropriate surgical strategy. Modification of the lifestyle or health factors that have led to IE are keys to improved long term outcomes.

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44

Prosthetic Valve Endocarditis

Bobby Yanagawa, Maral Ouzounian, and David A. Latter

High Yield Facts

- Prosthetic valve endocarditis (PVE) is an endovascular, microbial infection occurring on parts of a valve prosthesis or on reconstructed native heart valves.
- Early PVE is usually acquired perioperatively (nosocomial).
- Late PVE is mostly community acquired.
- Time cut off point between early and late PVE is roughly 120 days (notable differences in microbiology).
- The risk of early PVE is higher (approximately 5%) in patients with valve replacement during active infective endocarditis.
- Mechanical prosthesis infections originate from the sewing cuff or from nearby located thrombi → periprosthetic leaks, ring abscesses, invasion of adjacent tissue.
- Bioprosthesis infections mostly are restricted to the cusps → secondary bioprosthetic failure.
- Staphylococci, bacteria of the HACEK group, and fungi occur more frequently in PVE.
- Surgical management of PVE is complex due to the risk of sternal re-entry as well as the fact that infection commonly extends beyond the affected valve proper, resulting in abscess and fistula formation.
- The mainstay of PVE surgery is complete debridement of infective materials and repair or replacement of all damaged structures and re-replacement of valves.
- Aortic PVE frequently requires patch exclusion of abscess or fistula.
- Mitral PVE may require annular patch, which must be properly placed to avoid the devastating complication of atrioventricular disruption.
- The operative mortality for PVE varies widely from 10% to 60%.

Introduction

Prosthetic valve infective endocarditis (PVE) is a devastating complication of valve replacement resulting in valvular and paravalvular destruction leading to heart failure, embolism, sepsis and ultimately death [1] (Fig. 44.1). Prosthetic valve infection occurs in about 5% of patients with prostheses and accounts for roughly 25% of all cases of infective endocarditis [2, 3]. The annual incidence of PVE is approximately 1–3% with the highest incidence in the first post-operative year [4, 5]. Both bioprosthetic and mechanical valves are equally affected [6, 7].

Early PVE is defined as PVE within 120 days and late after 120 days. Approximately eighty percent of PVE occurs within the first 120 days [8]. Early PVE is the result of operative bacteremic seeding as well as from wound infections, urogenital infections, pneumonia, and line infections. Late PVE is most commonly due to systemic infection with highest risk in patients on hemodialysis and with a history of intravenous drug use (IVDU). Common etiologic agents for early PVE are coagulase negative Staphylococci, methicillin-resistant and sensitive *Staphylococcus aureus*, Enterococci, Gram-negative bacilli and Fungi, many of which are highly-resistant organisms [3, 5–10]. After 120 days, causative bacteremia are similar to native valve infective endocarditis (NVE), including an increase in Streptococci and coagulase-negative Staphylococci which are more likely to be associ-

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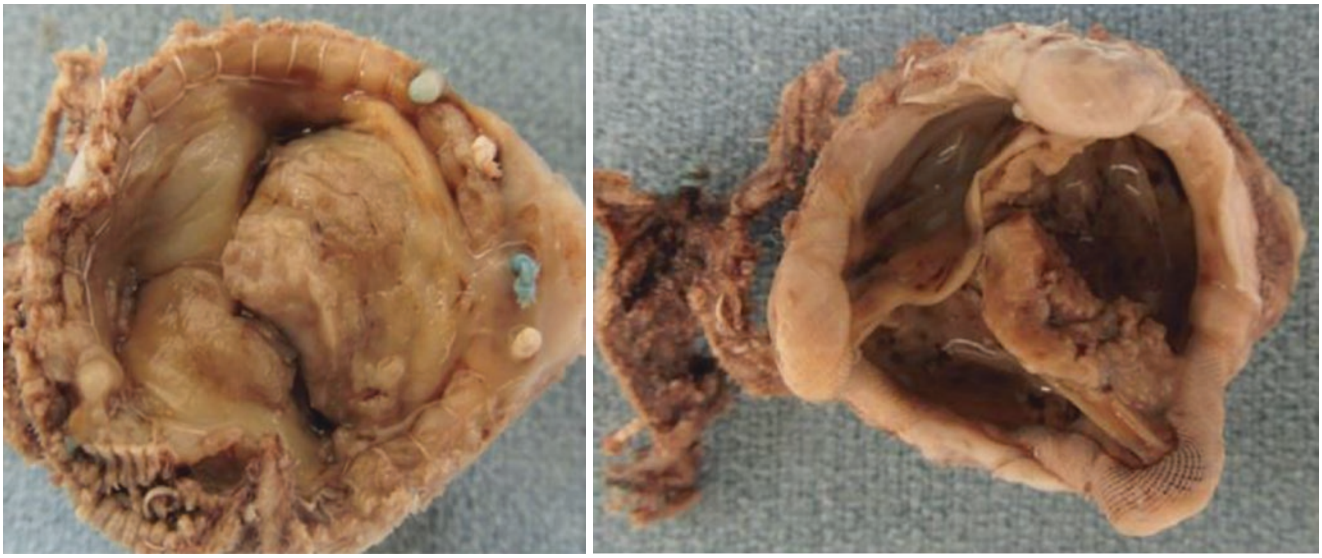


Fig. 44.1 Bovine pericardial bioprosthesis 2 years after implantation with extensive tissue damage and vegetations on all cusps

ated with skin infections and oral infections. Thus, current practice guidelines recommend appropriate prophylactic antibiotics for all patients with prosthetic valves undergoing procedures that can lead to significant bacteremia [11]. Culture-negative infective endocarditis varies between 15 and 40% in institutional series [9, 12]. Castillo et al. [13] found that culture-negative cases were more frequent in the first year after valve surgery. These findings could be due to administration of antibiotics prior to culture, administration of previous antibiotics or due to infection by fastidious bacteria such as HACEK, Fungi or Mycobacteria.

Surgical management is more frequently required for PVE than for NVE due to the resistant nature of infection of prosthetic materials [14]. These patients are often sicker and more complex than those with NVE due to delayed diagnosis, older age, critical hemodynamic state, resistant pathogens, recurrent embolism, congestive heart failure, renal failure, comorbidities, and others. Procedures require long pump runs and cross-clamp times due to the extensive adhesions from previous surgery and the need for more extensive debridement and cardiac reconstruction.

Imaging

Due to the high incidence of PVE in the first few post operative months, patients with fever and/or new valve dysfunction should be screened for IE with blood cultures and echocardiographic imaging without delay [14]. Echocardiography is the mainstay for diagnosis as it provides anatomic delineation of abscesses, fistulae, and prosthetic dehiscence. Transthoracic echocardiography is the first line imaging modality and often the superior imaging modality for a tricuspid prosthesis. Transesophageal echocardiography (TEE) is superior for imaging prosthetic aortic and mitral valves. Artifacts related to the presence of the prosthetic valve such as shadowing may be a challenge in interpretation of any echocardiographic images.

Computed tomography of the head, chest, abdomen and pelvis should be performed routinely prior to surgery for PVE. All patients with endocarditis undergoing surgery should have a CT head to rule out neurological injury, regardless of presence or absence of clinical neurological findings. CT chest is necessary to evaluate the risk of sternal re-entry. CT abdomen and pelvis is necessary to rule out peripheral embolism and abscess. ^{18}F-fluorodeoxyglucose positron emission tomography/CT is evolving as an important supplementary technique in difficult-to-diagnose cases of suspected PVE and NVE [15].

Coronary angiography should be considered to rule out coronary artery disease and/or coronary embolism. A coronary angiogram is strongly recommended for men over 50 years and post-menopausal women or in any younger patient with a high pre-test probability due to excessive cardiac risk factors. If there is any history of chest pain, ECG or biochemical evidence of ischemia or infarction, an angiogram is recommended to rule out coronary artery embolism. In patients with prosthetic aortic valve IE and presence of vegetation(s), there is a small risk of dislodgement of vegetation from the angiography wire and systemic embolism. The surgical and interventional team should discuss the risks and benefits of coronary angiogram and the utility of alternative procedures such as cardiac-gated CT angiogram in such patients.

Medical Management

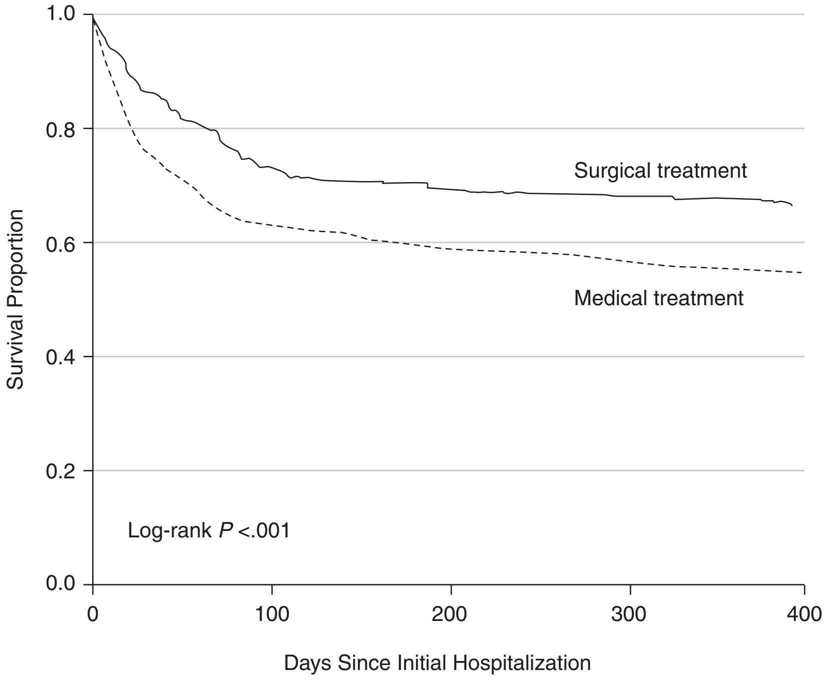
The first line for any IE is antibiotic management. Current guidelines recommend empiric treatment for early PVE and culture-negative cases with a combination of vancomycin, gentamicin, and rifampicin ± cefepime [14, 16, 17]. A small percentage of well-selected patients with PVE (e.g. uncomplicated PVE with Streptococcus infection) may clear an infection with antibiotics alone but most patients treated medically-only are deemed too high risk of surgery and their outcomes are poor [16]. Patients with acute valve dysfunction and heart failure, valve dehiscence, abscess development, recurrent embolization, or persistent bacteremia will require surgical replacement of the infected prosthesis. Moreover, due to the rapid progression of infection, a significant proportion of patients with PVE will require surgery on an emergency basis. In the International Collaboration on Endocarditis–Prospective Cohort Study (ICE-PCS), of 1025 patients with PVE, 47.8% underwent early surgery [3]. Early surgery was associated with lower in-hospital mortality (hazard ratio [HR]: 0.44, 95% confidence interval (CI): 0.38–0.52) and lower 1-year mortality (HR:0.57, 95%CI: 0.49–0.67), particularly in the higher risk cohorts (Fig. 44.2).

Surgical Management

The mainstay of PVE surgery is complete debridement of infective materials and repair or replacement of all damaged structures including any abscess or fistulous connections and re-replacement of excised prosthetic valves [17]. The operative mortality for PVE varies widely from 10% to 60% [18–24]. In early series, surgical mortality for PVE ranged from 20% to 60%, while most contemporary studies report a 30-day mortality below 15%. However, patients in critical condition or with complicated PVE, including periannular involvement or multiple valve involvement, still carry a very high operative mortality [6, 22–24]. Predictors of in-hospital mortality include increased age, female sex, longer bypass time during the operation, abscess, emergency surgery, poor hemodynamic status, staphylococcal infection, renal dysfunction, and multiple previous operations.

Prosthetic Aortic Valve Endocarditis

Briefly, our approach to any redo sternotomy is (1) review of previous operative notes, (2) careful review of the risk of re-entry on the CT chest, (3) mark, place wires, or surgically



No. at risk

	0	100	200	300
Surgery	490	287	255	239
Medical therapy	535	275	250	224

Fig. 44.2 Kaplan-Meier Curves for the cumulative probability of survival at 1 year with surgical and medical management of prosthetic valve infective endocarditis. (From Lalani T, et al. In-hospital and 1-year mortality in patients undergoing early surgery for prosthetic valve endocarditis. JAMA Intern Med. 2013;173:1495–504)

expose the femoral vessels according to the risk of re-entry, (4) four units of blood in the room and checked, (5) external defibrillation pads on the patient and (6) anesthesia and perfusion teams in the room—all prior to redo sternotomy.

We place the patient on pump, clamp and arrest the heart, and open the aorta to inspect the aortic root including the valve, aortic annulus, and surrounding structures. Our method of removal of a prosthetic aortic valve is the following: (1) We grasp a valve post, (2) use an 11- or 15-blade to cut directly down onto the sewing cuff of the valve starting anteriorly on the right sinus area to avoid inadvertent injury to the back wall of the left ventricular outflow tract and/or mitral valve, (3) use a combination of sharp dissection with scalpel and scissors to gently excise the valve while carefully cutting the native tissues as close to the prosthesis as possible. Once the valve prosthesis is removed, the annulus should be further debrided of all residual prosthetic valve material including pledgets and other obviously infected material or vegetations. The valve should be sent for culture and pathological examination. The aortic root, annulus, subvalvular outflow tract and mitral valve should be inspected for periannular or intramyocardial abscesses, defects or pseudoaneurysms and fistulae. If the infection is limited to the prosthetic valve, then the left ventricular outflow tract should be lavaged with a saline and bacitracin solution to remove debris and to rid the area of bacteria as much as possible. We recommend minimizing contamination of the infected field by changing surgical instruments and gloves after excision of all infected tissues. An appropriate prosthetic valve should then be implanted in the usual fashion. As with any reoperative aortic valve replacement (AVR), due to fibrosis the annulus is often contracted and less pliable. As such, root enlargement with a bovine pericardial patch is often necessary to facilitate implantation of an adequate sized prosthesis. In fact, annular and subannular abscesses that are located in the noncoronary area are most easily dealt with opening of the abscess cavity into the annulus and aortic root in a Manougian fashion and repaired with a pericardial patch that extends from the subannular area, across the annulus and into the aortic root. This facilitates surgical debridement, enlarges the annulus and makes the new valve implantation easier. Again, the Manougian technique with bovine pericardial patch allows for greater increase in annular size than the Nicks [25, 26].

Is There Any Advantage of a Homograft Versus Conventional Mechanical or Biological Prostheses?

Some surgeons have advocated for the use of cryopreserved homograft, particularly for PVE and for patients with extensive root abscesses, as they have been associated with lower risk of recurrent IE [27, 28]. The theoretic advantage of the homograft is resistance to infection as the graft is biologic and contains no artificial material. The STS practice guidelines suggest that it is reasonable to implant a conventional valve for aortic valve IE (Class IIa, Level of evidence B) and suggest homograft may be reasonable in patients with abscess or annular/aortic destruction (Class IIb, Level of evidence B) or for aortic PVE with abscess or extensive destruction (Class IIa, Level of evidence B) [29]. Our systematic review and meta-analysis showed no difference for patients receiving homograft vs. conventional prostheses in all-cause mortality (RR 0.95, 95% CI:0.67–1.33, $p = 0.75$ for unmatched and RR 0.82, 95%CI:0.36–1.84, $p = 0.63$ for matched studies), recurrent endocarditis (RR 0.90, 95% CI:0.44–1.84, $p = 0.77$ for unmatched and RR 1.04, 95% CI:0.49–2.19, $p = 0.92$ for matched studies) and reoperation (RR 1.60, 95% CI:0.80–3.21, $p = 0.18$ for unmatched and RR 3.17, 95% CI:0.52–19.44, $p = 0.21$ for matched studies) [30]. In our opinion, the type of valve implanted is less important than complete eradication of all infected and visually edematous tissues.

How Do We Approach an Aortic Perivalvular Abscess or Fistula?

The incidence of perivalvular extension ranges from 10% to 30% in native valve endocarditis and 30–50% in prosthetic aortic valve endocarditis. Aortic root abscess or destruction requires various degrees of repair, depending on the location and size and quality of the surrounding tissues. After exposing the aortic root and removing the prosthetic valve, one must carefully inspect the status of the coronary ostia, aortic wall, aortic annulus, anterior leaflet of the mitral valve, and ventricular septum. A defect in any of these key structures must be addressed. Any purulent tissue/fluid in an abscess cavity should be removed with an outside sucker, then the area should be debrided and copiously irrigated with a bacitracin-saline solution. Aggressive debridement of all infected tissues is mandatory for a successful operation for PVE. Depending on the timing of reoperative surgery and the extent of infection and destruction, differentiating between infected tissues and inflammatory phlegmon is not always straightforward. We recommend wide and radical excision of all edematous and potentially infected tissues.

A very small defect (e.g. 1–2 mm) in the aortic annulus may be excluded with pledgeted valve sutures. We almost always exclude annular and subannular abscesses with an oversized bovine pericardial patch and a running proline suture (Fig. 44.3). For large or multiple abscesses, one may consider a circumferential bovine pericardial patch to reconstruct the annulus followed by AVR (Fig. 44.4).

From the aortic root, anterior fistulas can connect the right sinus to the right atrium; alternatively, posterior connection from the left- or non-coronary sinus may fistulize to the left atrium. Subvalvular fistulas can connect the left ventricle to the right ventricle or the left ventricle to the right atrium

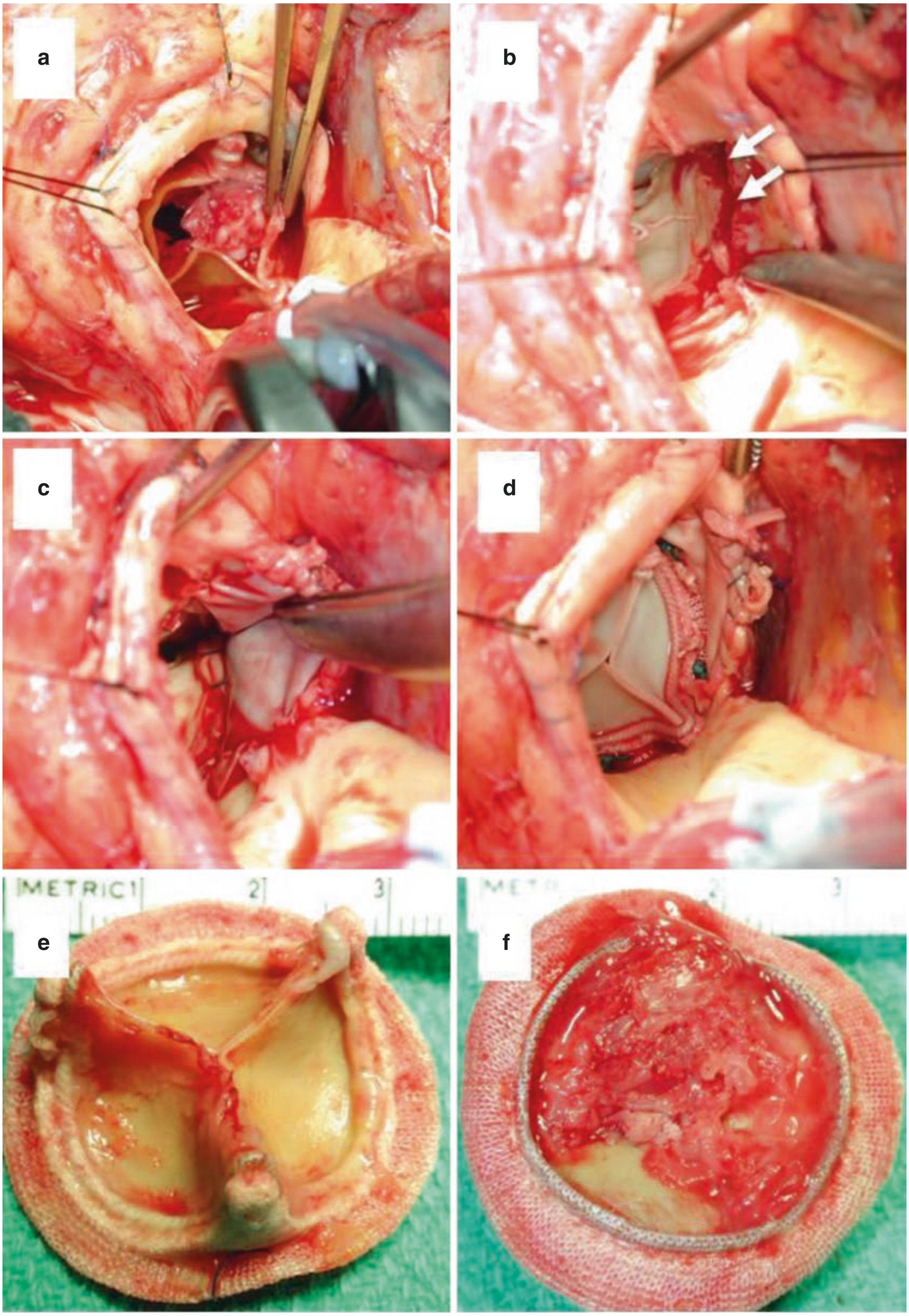


Fig. 44.3 Aortic prosthetic valve infective endocarditis. (**a**) Bioprosthetic valve visualized in situ with a large vegetation. (**b**) The valve has been removed revealing an annular abscess (arrows). (**c**) Bovine pericardial patch repair of abscess. (**d**) Re-replacement of aortic valve. (**e**) The aortic aspect of the explanted bioprosthesis is relatively intact. (**f**) There is a large, almost circumferential vegetation on the ventricular aspect of the valve

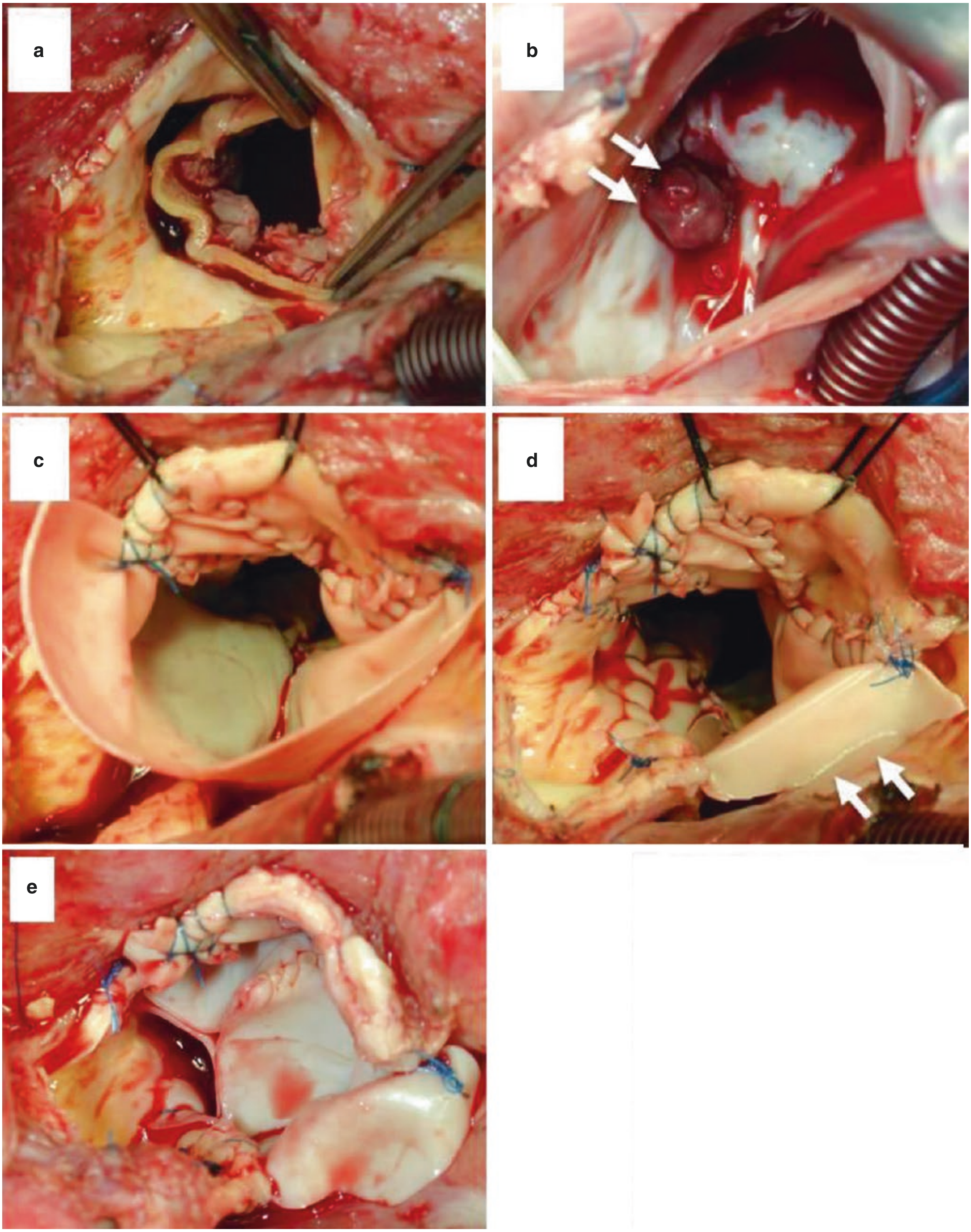


Fig. 44.4 Aortic prosthetic valve infective endocarditis. (**a**) Bioprosthetic valve visualized in situ with multiple vegetations. (**b**) The valve has been removed revealing an almost circumferential abscess with fistula (arrows). (**c**, **d**) Bovine pericardial patch repair of left and right coronary sinuses with Nicks root enlargement (arrows). (**e**) Re-replacement of aortic valve

(also known as a Gerbode defect). Any patient with a suspicion of a left-to-right fistula should have bicaval cannulation with caval snares. After removal of the prosthetic valve, any fistula from the aortic root or left ventricle should be identified and excluded with a bovine pericardial patch. The arterial pressure will push the patch against the aortic root or ventricular tissue and hold it in place. It is generally not necessary or possible to identify the opening of the fistula from the atrial or right ventricular surface of the fistula.

How Do We Approach an Aortic Root Abscess that Has Destroyed the Aorto-Mitral Continuity?

After removal of the prosthetic valve and resection of all infected tissues, one must make a decision on how much tissue is salvageable. Tomsic et al. [31] report on 35 patients that underwent surgery for extensive IE of the aortic valve with destruction of the aortic root, the aortic-mitral continuity and the mitral valve. The majority underwent aortic root replacement (91%), a minority underwent reconstruction of the aortic-mitral continuity and the roof of the left atrium using a folded pericardial patch. In 28 patients (80%), mitral valve repair was performed. For cases where the aorto-mitral curtain is completely destroyed and the mitral valve is infected, an aortic and mitral valve replacement with reconstruction of the intervalvular fibrous body, sometimes known as a Commando Procedure, may be needed [32, 33]. This represents a significant surgical challenge with high perioperative mortality and morbidity, and a high incidence of recurrent infection [34, 35].

What Is on the Horizon?

There are some novel surgical and transcatheter approaches for PVE that have been reported and may be considered. In recent years, use of sutureless prostheses has rapidly expanded due to the relative ease of implantation. Some groups have reported the use of the Perceval S (LivaNova, Saluggia, Italy) sutureless prostheses for prosthetic aortic valve endocarditis [36, 37]. There are a few advantages: (1) the avoidance of foreign material such as pledgets and threads, (2) a large effective orifice area and (3) the ability of these devices to seal against a fibrotic and scarred annulus and (4) a reduction in bypass and cross-clamp times. Similarly, a successful valve-in-valve transcatheter aortic valve replacement (TAVR) performed surgically under direct visualization has been described in a patient with homograft aortic valve endocarditis [38]. It is important to reiterate that this can only be performed after all the infected material has been debrided.

Prosthetic valve infective endocarditis after TAVR has been reported to occur with an incidence of 0.5–3% per patient-year and it is associated with high mortality rates [39, 40]. As TAVR is currently offered to high- and intermediate-patients, an operative procedure for infection of the TAVR device carries considerable risk. In the Infectious Endocarditis after TAVR Registry, the in-hospital mortality rate for patients with IE following TAVR was 36% and surgery was performed in 14.8% of patients. There is a limited benefit of surgery likely reflective of the high or prohibitive surgical risk of these patients, in addition to the potential technical difficulties of removing a stent frame adherent to the aorta. With the expanded indication of TAVR to eventually low risk patients, reoperation for infected TAVR devices necessitating removal of the devices and possible reconstruction of the aortic root will likely become a reality.

Mitral and Tricuspid Prosthetic Valve Endocarditis

We access the mitral prosthesis in the usual left atriotomy approach. The valve is grasped and an 11 or 15-blade is used to cut down to the sewing cuff. The valve is peeled out progressively and removed. A risk with any reoperative mitral valve surgery is AV groove disruption. One must remove the valve without inadvertent removal of the mitral annulus. The annulus and subannular apparatus should be carefully inspected for abscesses, calcification and damage followed by removal of a prosthetic mitral valve.

Outcomes are worse for surgical treatment of mitral compared with aortic valve PVE, due to the inability to perform radial debridement in the atrioventricular groove [41]. If the mitral annulus is infected or damaged, the affected area must be re-approximated using plegeted valve sutures or reconstructed using a bovine pericardial patch to cover the area of debridement ensuring endocardial continuity to prevent the devastation of atrioventricular dissociation. After mitral annular patch reconstruction, we use “non-everting” interrupted horizontal mattress sutures with pledgets through the patch. Reconstruction of the left ventricle risks damage to the circumflex coronary artery in the area of P1–P2. Any new lateral wall motion abnormalities suggest such injury and should be managed with a vein graft to the lateral wall. A small annular defect can be addressed using “non-everting” plegeted valve sutures carefully placed into the ventricular myocardium and on the atrial endocardium outside of the reconstructed annulus.

Mitral valve homograft is rarely performed but has been described for prosthetic valve infective endocarditis for drug-resistant endocarditis or for mitral valve IE in IV drug users. If the aortic valve is involved requiring extended resection of the diseased tissue, aortomitral fibrous body reconstruction and double valve replacement may need to be performed. An aortomitral homograft has been described but should be considered experimental [42].

Surgical re-replacement for tricuspid PVE is generally technically straightforward. This occurs most frequently in the IVDU population. There are ethical issues on the role of surgical re-replacement, particularly in the context of recidivism of drug use [43].

Prosthetic Valve Endocarditis of Aortic Graft

Infection of an aortic graft is a devastating complication and reported to occur between 1% and 4% [44–46]. Early infection occurs by direct intraoperative contamination and late infection usually resembles NVE [47, 48]. Treatment with antibiotics alone is usually insufficient to resolve the infection especially in the presence of periprosthetic abscesses. Lifelong antibiotics are reserved for patients who are deemed inoperable. In patients with a supracoronary graft and AVR, the infection is more frequently located on the valve rather than on the conduit. In such cases, we recommend re-replacement of the infected prosthetic valve as well as aortic graft. For overt infection of an aortic graft itself, surgical intervention can be limited to the resection of graft vegetation or complete replacement of the vascular prosthesis. Here, debridement of all infected tissues is followed by re-replacement with a Dacron graft or homograft. Adjunctive measures include local graft coverage with omentum or muscle flaps, use of perigraft catheters for antibiotic irrigation. The Coselli group advocate for use of homograft and for lifelong suppressive antibiotic therapy following any aortic graft replacement for IE [47].

Conclusion

Prosthetic valve infective endocarditis remains a challenging complication of valve replacement. In the aortic position, surgical management may require management of abscess and fistula as infection often extends beyond the valve proper. Mitral PVE is a challenge as debridement beyond the annulus places the patient at risk of atrioventricular dissociation. More recently groups are reporting PVE with the use of novel percutaneous valve interventions such as transcatheter aortic valve replacement and Mitraclip. For the foreseeable future, PVE will require complex and high-risk surgical management. Novel devices such as sutureless aortic valves may offer some advantages in select patients.

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Tricuspid Valve Surgery

45

Christoph T. Starck and Volkmar Falk

High Yield Facts

- In developed countries the most common tricuspid pathology is regurgitation, while tricuspid stenosis is extremely rare.
- Tricuspid regurgitation (TR) can be of primary or secondary origin.
- Secondary or functional tricuspid regurgitation is the most frequent cause of tricuspid insufficiency.
- In symptomatic patients with isolated severe tricuspid valve stenosis surgery is indicated (Class I).
- Concomitant to left-sided valve surgery tricuspid valve surgery is indicated in case of patients with severe primary or secondary tricuspid regurgitation (Class I).
- Surgery should be considered either in the case of moderate primary TR or in patients with mild to moderate TR with dilated annulus (≥40 mm or >21 mm/m^2) in case of left-sided valve operations (Class IIA).
- Tricuspid valve surgery can either be performed on beating heart or with cardioplegic cardiac arrest.
- Functional tricuspid regurgitation can be characterized into three different stages and surgical management should be tailored to these stages.
- In case of significant leaflet tethering augmentation of the anterior tricuspid leaflet should be performed in addition to a ring annuloplasty.

Introduction

The tricuspid valve, sometimes also referred to as the "forgotten valve", remains undertreated, even though severe tricuspid regurgitation (TR) can cause relevant symptoms and is associated with decreased survival [1–3].

In developed countries the most common tricuspid pathology is regurgitation, while tricuspid stenosis is extremely rare (Table 45.1). Tricuspid regurgitation can be of primary or secondary origin [4]. The underlying cause of primary TR is a leaflet pathology and some congenital disorders such as Ebstein's anomaly. Secondary or functional TR (FTR) is the most frequent cause of tricuspid insufficiency [5]. FTR may be caused by annular dilatation as well as right ventricular enlargement and dysfunction as a consequence of left-sided heart disease from valvular or myocardial causes, right heart infarction or right ventricular pressure and volume overload (caused by pulmonary hypertension, cardiomyopathies and other reasons) [1, 4, 6] (Table 45.2). Long-standing persistent or permanent atrial fibrillation may lead to the development of FTR by its effect on tricuspid annular dilatation [1, 6].

Surgical treatment of FTR in the context of left-sided valvular disease remains a matter of controversy with regards to accurate diagnosis, indications for surgery, surgical techniques and the late outcomes of surgical interventions [5]. In the current era of percutaneous valve interventions transcatheter option for treatment of tricuspid valve disease is evolving. Transcatheter tricuspid valve therapy is at an early stage and has so far not reached routine clinical practice [7, 8].

Indications for Tricuspid Surgery

All recommendations on the indications for tricuspid valve surgery in the current ESC/EACTS guidelines on the management of valvular heart disease are merely based on expert opinion [4].

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Table 45.1 Causes of tricuspid stenosis

Immunological disease
Rheumatic heart disease
Antiphospholipid sysndrome
Systemic lupus erythematosus
Infection
Infective endocarditis (large vegetations)
Tumors
Myxoma
Carcinoid syndrome
Intravenous leiomyomatosis
Renal cell carcinoma
Ovarian tumors
Congenital abnormalities
Ebstein's anomaly
Metabolic or enzymatic abnormalities
Fabry's disease
Whipple's disease
Drugs
Fenfluramine/phentermine
Methysergide
Iatrogenic
Ventriculoatrial shunts
Fusion of ICD or PPM leads to sub-valvular structures

ICD implantable cardioverter defibrillator, *PPM* permanent pacemaker

Table 45.2 Causes of tricuspid regurgitation

Primary tricuspid regurgitation
Congenital abnormalities
Ebstein's anomaly
Tricuspid valve dysplasia, hypoplasia, or cleft
Double orifice tricuspid valve
Acquired disease
Endocarditis
Rheumatic disease (with left-sided disease)
Carcinoid syndrome
Drugs
Serotonin-active drugs
Degenerative
Tricuspid valve prolapse, flail
Iatrogenic
Radiation
Cardiac device (PPM, ICD) leads
Right ventricular endomyocardial biopsy
Degenerated bioprosthesis
Trauma
Blunt chest wall trauma
Secondary tricuspid regurgitation
Diseases affecting the right ventricle and tricuspid annulus
Right ventricular and tricuspid annular dilatation
Left-sided valvular and/or myocardial disease
Pulmonary hypertension independent of left-sided cardiac pathology
Right ventricular infarction with remodelling
Chronic right ventricular pacing (dyssynchrony)
Atrial fibrillation

ICD implantable cardioverter defibrillator, *PPM* permanent pacemaker

In symptomatic patients with isolated severe tricuspid valve stenosis (TS) surgery is indicated (Class I). Regardless of the presence of symptoms tricuspid surgery is indicated in patients with severe TS undergoing left-sided valve interventions.

With regard to the surgical indications for the treatment of TR, different indications for isolated tricuspid procedures and concomitant tricuspid procedures in the context of the surgical correction of left-sided valve pathologies exist.

In symptomatic patients with severe isolated primary TR without severe right ventricular dysfunction surgery is indicated (Class I). Surgery should be considered in asymptomatic or mildly symptomatic patients with severe isolated primary TR as well as deterioration of right ventricular function or progressive right ventricular dilatation (Class IIA). After left-sided valve surgery and in the absence of recurrent left-sided valve dysfunction, isolated tricuspid valve surgery should be considered in patients with severe TR, who are either symptomatic or show progressive right ventricular dilatation or dysfunction, in the absence of severe right or left ventricular dysfunction, or severe pulmonary vascular disease/hypertension (Class IIA).

Concomitant to left-sided valve surgery tricuspid valve surgery is indicated in case of patients with severe primary or secondary TR (Class I). Surgery should be considered either in the case of moderate primary TR or in patients with mild to moderate TR with dilated annulus (≥40 mm or >21 mm/m^2) in case of left-sided valve operations (Class IIA). Patients undergoing left-sided valve surgery and presenting with mild or moderate TR in the absence of annular dilatation, but with documented previous right-heart failure may be considered for concomitant tricuspid surgery (Class IIB) [4].

Surgical Techniques for Tricuspid Valve Surgery

General Considerations

Isolated tricuspid surgery can be performed with cardioplegic cardiac arrest or on beating heart.

The patient is put on cardiopulmonary bypass with bicaval venous cannulation. After snaring of both caval veins, a right atriotomy can be performed. In case of a beating heart approach venous drainage from the coronary sinus is controlled by placing a vent in the ostium of the coronary sinus.

Both tricuspid repair and replacement can also be performed minimally invasive through a 5 cm right lateral thoracotomy.

Tricuspid Valve Repair

Several techniques for an individualized surgical treatment of the various tricuspid valve pathologies exist. Surgical techniques can be divided into different categories (Table 45.3) with regard to the involved anatomical structures (annulus or leaflets). If repair is impossible or the result is not satisfactory, tricuspid valve replacement is performed.

Annuloplasty Techniques

The "classic" De Vega annuloplasty consists of a plication of the posterior and anterior portion of the annulus with a double continuous suture, preserving the septal portion of the annulus. This technique was developed in the early 1970s and has been one of the most frequently used techniques for surgical correction of FTR [5]. Several modifications have been proposed (e.g. Antunes and Girdwood, Sarray and Duarte) [9, 10].

At present, the most frequently performed procedure for repairing FTR secondary to tricuspid annular dilatation is undersized prosthetic tricuspid annuloplasty with devices such as flexible bands, rigid or semirigid annuloplasty rings (Fig. 45.1). The current generation of tricuspid annuloplasty rings features a three dimensional design that respects the non-planar geometry of the native tricuspid annulus. As opposed to mitral rings, tricuspid rings are not closed and spare the native annulus at the level of the triangle of Koch to avoid AV-block. The undersized prosthetic tricuspid annuloplasty technique remodels the annulus, increases leaflet coaptation and reduces recurrent annular dilatation [5].

Table 45.3 Current techniques for surgical treatment of tricuspid valve disease

Category	Techniques
Annuloplasty techniques	• Prosthetic ring/band annuloplasty • De Vega annuloplasty
Leaflet repair techniques	• Tricuspid leaflet augmentation • Clover technique
Other surgical repair techniques	• Double orifice valve technique • Posterior annular bicuspidization
Tricuspid valve replacement	• Prosthetic tricuspid valve replacement (mainly biological) • Extracellular matrix cylinder

Leaflet Repair Techniques

The "clover technique" was described by De Bonis et al. and is similar to the Alfieri repair technique for mitral valve repair. The central part of the free edges of the tricuspid leaflets are sutured together producing a clover-shaped valve; it is always combined with a prosthetic ring annuloplasty. The objective of this approach is to improve the efficacy of tricuspid valve repair in the setting of complex degenerative or post-traumatic pathologies [5, 11].

In case of leaflet tethering in addition to tricuspid annular dilatation the leaflet augmentation technique described by Dreyfus et al. increases the surface of leaflet coaptation by threefold and brings the coaptation zone down into the right ventricle at the level of the tethered posterior and septal leaflets, while maintaining leaflet mobility. To achieve this the anterior leaflet is first detached from the anterospetal to the anteroposterior commissure and then enlarged by the use of an autologous pericardial patch (Fig. 45.2) [5, 6, 12, 13].

Other Surgical Techniques

The rationale for posterior annular suture bicuspidization is the finding that the primary anatomic problem in FTR is dilatation of the posterior tricuspid annulus [12]. The suture bicuspidization is performed by placing a double-pledget-supported mattress suture from the anteroposterior to the anteroseptal commissure along the posterior annulus (Fig. 45.3) [14].

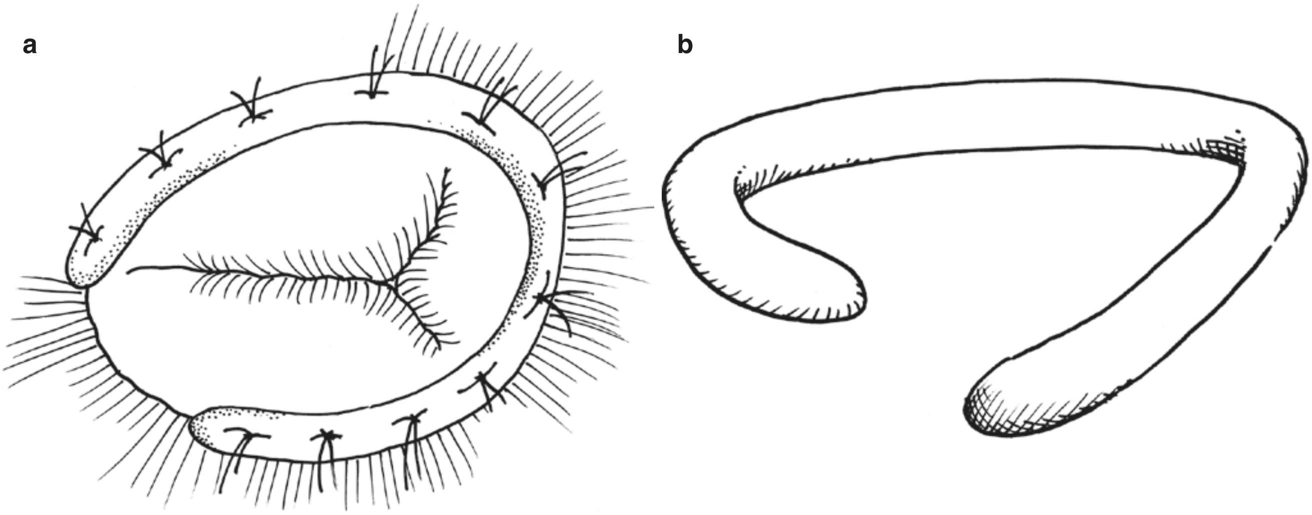

Fig. 45.1 Prosthetic tricuspid ring annuloplasty. (**a**) The ring is open at the level of the triangle of Koch to avoid the occurrence of AV-block. (**b**) The current generation of tricuspid annuloplasty rings feature a 3D-design that respects the non-planar geometry of the native tricuspid annulus

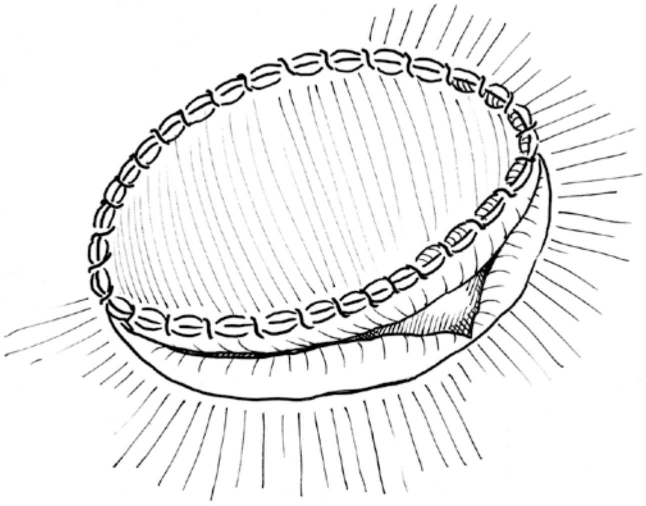

Fig. 45.2 Leaflet augmentation technique. The anterior leaflet is first detached from the anteroseptal to the anteroposterior commissure and then enlarged by the use of an autologous pericardial patch

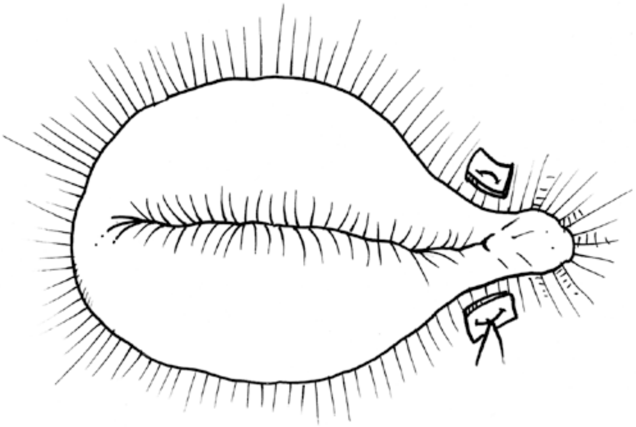

Fig. 45.3 The posterior annular bicuspidization is performed by placing a double-pledget-supported mattress suture from the anteroposterior to the anteroseptal commissure along the posterior annulus

The double orifice valve technique is performed by passing two pledget-supported mattress sutures from the middle of the anterior annulus to the septal annulus, aiming at a point located at two-thirds of the length of the septal annulus measured from the anteroseptal commissure to avoid injury to the bundle of His (Fig. 45.4).

Tricuspid Valve Replacement

If valve repair is impossible or if the result of a repair attempt is not satisfactory tricuspid valve replacement needs to be carried out. In more advanced forms of tethering and right ventricular dilatation, valve replacement should be primarily considered. Currently the use of large-sized bioprostheses is favored over valve replacement with mechanical valves [4, 15].

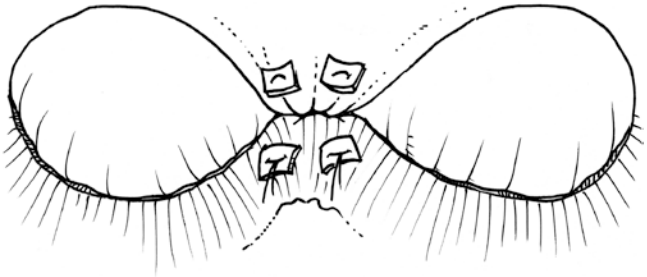

Fig. 45.4 The double orifice valve technique is performed by passing two pledget-supported mattress sutures from the middle of the anterior annulus to the septal annulus

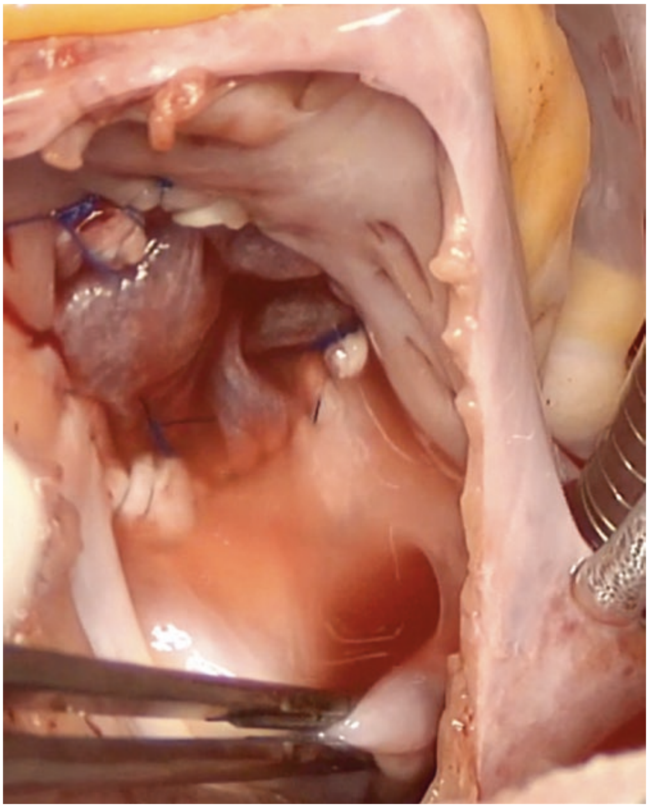

Fig. 45.5 Tricuspid valve replacement with the use of an extracellular matrix cylinder in a patient with tricuspid valve endocarditis

Gerdisch et al. have described a tricuspid valve replacement technique using an extracellular matrix cylinder in patients with tricuspid valve endocarditis with promising results (Fig. 45.5) [16].

Results of Surgical Techniques

Functional TR was often undertreated in the past. It was thought that surgical correction of left-sided valvular heart disease would sufficiently improve FTR by reducing pulmonary hypertension and volume overload. Furthermore, there was uncertainty about the optimal tricuspid valve repair technique and a substantial rate of repair failure was reported [17].

Based on data from current literature it has become evident that left-sided valvular operations do not necessarily lead to an improvement of FTR and more importantly that residual TR is a prognostic factor for poor long-term outcome. Residual TR after mitral valve surgery is associated with an approximately 50% decrease in 5-year survival. It was also found that persistent TR is an independent predictor of development of heart failure with a hazard ratio of 2.46 [17–19]. Concomitant tricuspid valve annuloplasty in mitral valve surgery, with the indication based on the extent of tricuspid annular dilatation irrespective of the grade of regurgitation, leads to a significant improvement in functional status and prevents the development of remarkable regurgitation in the further course [20].

Surgical treatment of FTR has been focused on correction of annular dilatation over many years. Surgical strategies have changed with a more sophisticated and pathology based approach to the treatment of FTR, but annuloplasty still remains a key component.

The impact of ring versus suture (de Vega) annuloplasty on short-term outcomes, mortality and TR recurrence was investigated in a meta-analysis. Freedom from recurrent moderate TR at 15 years was significantly better in patients with ring annuloplasty (78.9 ± 5.0% versus 50.5 ± 5.9%; $p = 0.0107$) without significant impact on 15 years-survival between the two groups (Ring annuloplasty: 48.0 ± 4.6% versus Suture annuloplasty: 34.6 ± 4.7%; $p = 0.441$) [21].

Ren et al. compared the results of De Vega annuloplasty with ring annuloplasty in 74 patients with concomitant left-sided valve operations in a retrospective analysis. Complications and in-hospital mortality (2.9% DeVega versus 2.5% ring annuloplasty) were similar in the two groups ($p = 0.6755$). Freedom from recurrent TR was significantly better in the ring annuloplasty group at 1 month, 6 months, 1 year, 2 years (log rank $p = 0.0377$) [22].

Tricuspid valve surgery can either be performed on beating heart or with cardioplegic cardiac arrest. Besides reducing time of myocardial ischemia, another advantage of the beating heart approach is the possibility to assess the occurrence of atrioventricular block during the procedure. Baraki et al. compared the outcomes of 92 patients who underwent isolated tricuspid valve operations either with beating or arrested heart approach. Perioperative outcomes and 30-day mortality did not differ between the two groups. Freedom from reoperation at 10 years was significantly lower in the beating heart group (arrested heart: 95% versus beating heart: 70%; $p = 0.039$) [23].

Recurrent or residual TR is a common finding after isolated annuloplasty. McCarthy et al. investigated the outcomes of 790 patients with tricuspid valve annuloplasty using different techniques. Relevant TR (grade 3+ and 4+) was present in 14% patients at 1 week postoperatively [24%]. Based on these findings it is evident that relying merely on annuloplasty techniques for the correction of FTR may not be sufficient.

Surgical treatment of FTR needs to be performed with a more individualized approach. FTR should be classified into three different stages. The first stage is defined as mild TR without annular dilatation (annular diameter <40 mm) and normal leaflet coaptation. The second stage is characterized by annular dilatation (annular diameter >40 mm) and impaired leaflet coaptation (only at the edge level), leading to mild or moderate regurgitation. The third stage of FTR shows severe TR, annular dilatation and impaired leaflet coaptation with leaflet tethering as well as a tenting height of at least 8 mm below the plane of the annulus [5, 6, 13]. Surgical therapy should be tailored to the stages of the disease. Stage 1 does not require surgical intervention. In stage 2 valve annuloplasty is recommended and most likely sufficient to restore leaflet coaptation. In stage 3 FTR, in addition to annuloplasty augmentation of the anterior tricuspid leaflet is recommended to provide a sufficient coaptation surface, which will ensure good long-term outcomes and avoid recurrent TR [6].

Another underestimated but important aspect of surgical management of tricuspid valve disease is to address transvalvular pacemaker or implantable cardioverter defibrillator (ICD) leads. Trans-tricuspid pacemaker leads are an independent risk factor for late recurrence of TR. At 5 years after tricuspid valve annuloplasty 42% of the patients with a transvalvular pacemaker lead showed relevant TR compared to 23% of the patients without a pacemaker [24]. This finding suggests that late repair failure may be reduced by removing trans-tricuspid leads and replacing them with epicardial leads at the time of tricuspid valve surgery [1] or a transvenous coronary sinus lead in the further course. This aspect of pacemaker and ICD lead management also applies to biological tricuspid valve replacement.

Conclusion

Tricuspid valve surgery in developed countries is mostly performed for the treatment of functional tricuspid valve regurgitation. In this context, the cornerstone of current surgical techniques is ring annuloplasty. Functional tricuspid regurgitation can be characterized into three different stages and surgical management should be tailored to these stages. In case of significant leaflet tethering augmentation of the anterior tricuspid leaflet should be performed in addition to a ring annuloplasty.

Acknowledgment *Conflict of Interest Statement*: The authors declare no conflict of interest.

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Minimally Invasive Aortic Valve Surgery

46

Mattia Glauber and Antonio Miceli

High Yield Facts

- Aortic valve disease is the most common cardiovascular problem in the developed countries and its incidence is likely to increase with age.
- Data reported from the Society of Thoracic Surgeon (STS) database have shown a dramatic reduction in in-hospital mortality from 3.4% in 1997 to 2.6% in 2006 for isolated aortic valve replacement (AVR).
- The most common minimally invasive approach for AVR is the partial upper ministernotomy followed by the right anterior minithoracotomy.
- Compared with conventional surgery, minimally invasive aortic valve surgery has been shown to reduce postoperative mortality and morbidity, providing faster recovery, shorter hospital stay, better cosmetics results and less wound infection.
- Minimally invasive AVR using sutureless or rapid deployment valves reduces cross clamp and CPB times.
- With the introduction of sutureless valves, the operative mortality of minimally invasive AVR patients has decreased from 1.6% to 0.7% in a 7 year period.
- Minimally invasive AVR with a sutureless prosthesis may be considered an "alternative" to TAVI procedure for high-risk "operable patients".

Introduction

Aortic valve disease is the most common cardiovascular problem in the developed countries and its incidence is likely to increase with age [1]. Aortic valve replacement (AVR) via full sternotomy is the gold standard surgical therapy for patients with severe aortic stenosis (AS) and insufficiency [1]. This procedure has proved to be reliable, reproducible, relieves symptoms and improves prognosis of the patients. Improvements in anesthesia, surgical techniques, postoperative care and strategies of myocardial protection have allowed surgeons to treat patients with advanced age and or comorbidities safely with a low rate of morbidity and mortality. Data reported from the Society of Thoracic Surgeon (STS) database have shown a dramatic reduction in in-hospital mortality from 3.4% in 1997 to 2.6% in 2006 for isolated AVR [2]. AVR through full sternotomy is the conventional approach for the treatment of aortic valve disease. However, in recent years minimally invasive aortic valve surgery (MIAVS) is being increasingly performed in many centres and has now become an alternative to full sternotomy AVR in an attempt to reduce the "invasiveness" of the surgical procedure, while maintaining the same efficacy, quality and safety that is associated with the conventional approach.

Definition, Surgical Approaches and Rationale for MIAVS

Patients have become older with multiple comorbidities and this population is expected to expand. Less-invasive procedures are known to reduce the number of complications and the smaller incisions cause less pain, less blood loss and reduced length of hospital stay.

The Society of Thoracic Surgeons (STS) database defines minimally invasive cardiac surgery as "any procedure not performed with a full sternotomy and cardiopulmonary (CPB) support" [3, 4]. Transcatheter aortic valve implantation (TAVI) is a prototype of minimal access aortic valve replacement. TAVI offers an alternative treatment option in high-risk patients, having been demonstrated to be superior to medical therapy in non-operable patients and non-inferior to surgical aortic valve replacement. However, controversies still exist regarding its effect on postoperative outcomes

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compared with conventional surgery. A meta-analysis of randomized controlled trials that included 3828 patients with severe AS found no significant differences between TAVI and conventional AVR in terms of myocardial infarction, stroke and mortality. Conversely, a sub-group analysis showed a higher incidence of vascular complications, neurological events, aortic regurgitation and need for permanent pacemaker implantation in patients undergoing TAVI [5].

Nevertheless, in 2008, a scientific statement from the American Heart Association defined minimally invasive cardiac surgery "a small chest wall incision that does not include the conventional full sternotomy". We will use this latter definition as we believe that the term "minimally invasive cardiac surgery" is a "concept" or a "philosophy" that aims to reduce the degree of surgical invasiveness without being procedure-specific [6].

The most common minimally invasive approach is the partial upper ministernotomy followed by the right anterior minithoracotomy (Fig. 46.1). Other less-invasive techniques include a right parasternal approach from the second to the fourth costal cartilages and transverse sternotomy.

MIAVS was first performed through a 10 cm right parasternal approach in 1996 at the Cleveland Clinic Foundation by Cosgrove and Sabik [7]. This technique consisted of removing the second, third and fourth costal cartilages as well as sacrificing the right mammary artery. The major limitation of this technique was a high incidence of lung herniation that was physiologically disturbing and cosmetically disfiguring, often requiring a second operation to repair the defect. This approach was soon abandoned in favour of ministernotomy approach [8].

Compared with conventional surgery, MIAVS has been shown to reduce postoperative mortality and morbidity, providing faster recovery, shorter hospital stay, better cosmetics results and less wound infection. In addition, MIAVS has been shown to improve postoperative respiratory function due to the preservation of sternum, reduced postoperative pain, blood loss and blood transfusions related to the reduction of surgical dissection, and facilitates reoperation at a later date, as part of pericardium remains closed. Finally, MIAVS requires less rehabilitation resources that translates into cost reduction [9–13].

Preoperative assessment for MIAVS should be the same as for other cardiac operations. The severity of comorbidities should be known and pre-existing health conditions require thorough work-up. Multidisciplinary team discussions and detailed preoperative planning allow better outcomes for patients. Effective preoperative planning is essential to identify any further complications prior to surgery that could delay patient recovery. Preoperative conditions such as chronic lung diseases, cerebrovascular disease, peripheral arterial disease, chest wall abnormalities, lung irradiation and previous cardiac/lung surgery are especially relevant when minimally invasive approaches are being contemplated. Routine preoperative evaluation tests such as electrocardiogram, chest X-ray, complete bloods, echocardiogram and angiogram are performed in the usual manner as for full sternotomy counterparts. Additionally, computed tomography (CT) scan plays an important role for decision making in terms of the approach. CT allows better understanding of the anatomy and provides valuable information about the lungs, airway, chest wall and mediastinum, including heart and

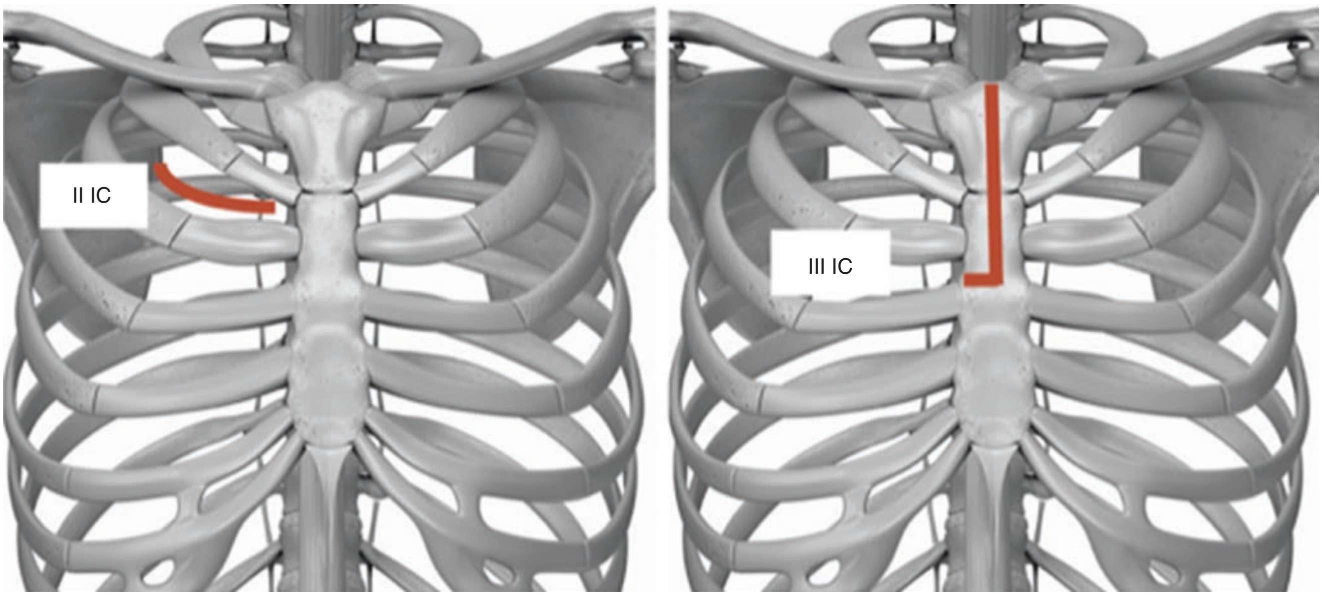

Fig. 46.1 Minimally invasive approaches. (Left) Right anterior minithoracotomy; (Right) Ministernotomy. *II IC* second intercostal space, *III IC* third intercostal space

great vessels. Entities such as lung adhesions, diaphragm paralysis and chest wall abnormalities namely scolisosis, pectus carinatum or pectus excavatum can make the procedure challenging and affect a change in the initial planned approach. In patients with previous cardiac surgery or chest wall irradiation, a chest CT conveys the distance between the posterior sternal table and right ventricle. The presence of patent coronary bypass grafts crossing the midline is particularly hazardous. For the upper half sternotomy approach, CT scan confirms to which intercostal space to extend the J.

For the right anterior minithoracotomy approach, the CT scan also facilitates important information regarding the aorta and the relationship with the sternum. By noting which intercostal space is closest to the tip of the right atrial appendage, the preferred intercostal space is identified for the right anterior minithoracotomy approach. In essence, the right anterior minithoracotomy procedure is more favourable if:

- The aorta lies more than one-half to the right of a vertical line drawn from the right sternal border to the ascending aorta in the axial CT view; and
- The distance is less than 10 cm from the skin to the ascending aorta where the pulmonary artery bifurcates (Fig. 46.2).

Peripheral vascular and cerebrovascular disease increases the risk of stroke and embolization. Careful assessment of the vascular system is carried out. CT angiogram is performed if suspicious or elevated risk of stroke or embolization due to retrograde perfusion through peripheral cannulation is anticipated. Atherosclerosis and calcium plaques in the ascending aorta suggest choosing a different cannulation site. A smooth, calcified plaque is less hazardous than a soft or irregular plaque. In addition, the relative size and tortuosity of the iliofemoral vessels on angiogram are important factors in selecting the appropriate arterial cannula. Sealant devices, such as angio-seal®, are not recommended after preoperative angiogram because femoral cut-down and subsequent cannulation of the femoral artery becomes arduous. In a patient with a history of stroke or transient ischemic attack, duplex scanning of the carotid and vertebral arteries is obtained.

Preoperative Anaesthetic Considerations

Anaesthetic considerations for MIAVS should be as for any other cardiac surgical procedure. To facilitate rapid extubation a short acting drugs based anaesthesia should be considered. A central venous multi-lumen catheter should be used and jugular sheath for possible temporary pacing via jugular access should be planned. External defibrillator pads should be placed due to limited access to the heart for internal defibrillation.

Minimally invasive aortic valve replacement (MIAVR) requires a good coordination between surgeon, perfusionist, anaesthesiologist, cardiologists and nurses to achieve the best clinical outcomes. Intraoperative transesophageal echocardiography (TEE) is used routinely. A pulmonary artery catheter is employed based on patient risk and the specific

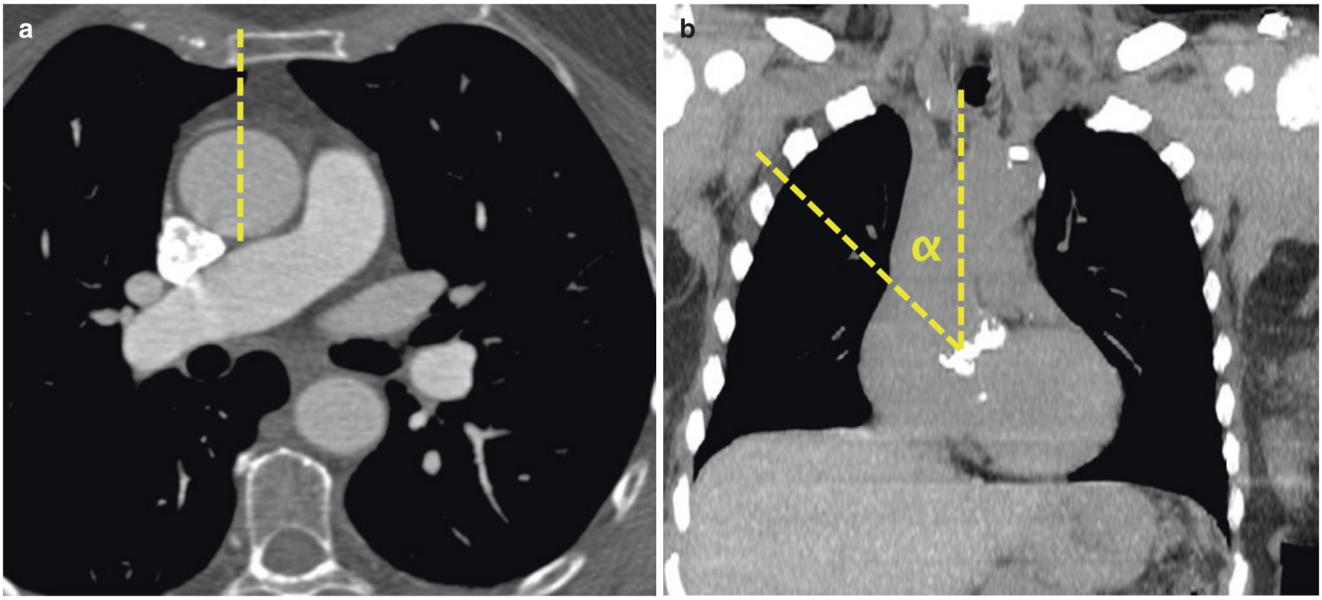

Fig. 46.2 Right thoracotomy rules. (**a**) At the level of main pulmonary artery, the ascending aorta is rightward (more than one half located on the right with respect to the right sternal border) and the distance from the ascending aorta to the sternum does not exceed 10 cm; (**b**) The α angle (angle between the midline and the inclination of ascending aorta) should be >45°

operation. For both ministernotomy and right anterior minithoracotomy, a single lumen endotracheal tube is standard. To achieve optimal exposure during right anterior minithoracotomy, the right lung can be mechanically retracted posteriorly without the need to resort to single-lung ventilation. However, right lung isolation can be useful during the learning curve and in difficult cases using double lumen endotracheal tube or bronchial blocker. To improve emptying of the heart during CPB, vacuum-assisted or kinetic venous drainage is commonly used. The patient is positioned supine and surgically prepped from the neck to mid-thigh for both procedures. External defibrillator pads are placed similarly to redo surgery. The mandatory use and routine interpretation of the intraoperative TEE for de-airing process is a critical step at the end of CPB in any MIAVS procedure. The echocardiogram images are visualised and evaluated at the actual time of the operation; this is performed in the same manner as in the conventional full sternotomy approach. Completely de-aired heart will allow weaning of CPB and transition to the end of the procedure with minimal microembolisation.

Ministernotomy and Right Anterior Minithoracotomy

The ministernotomy approach represents the most common technique used for MIAVR. The ministernotomy approach is achieved through 6- to 8-cm midline vertical skin incision, performing a partial J sternotomy at the second, third or fourth intercostal space; an inverted T or V-shaped ministernotomy at the level of the second or third intercostal space can be chosen as an alternative [3, 13].

A sternal saw is used and the right internal thoracic artery is spared. A rigid retractor with narrow blades is inserted. Central aortic cannulation is straightforward but should be aimed as distal as possible to provide an unencumbered working space. In case of concomitant ascending aorta replacement a femoral cannulation can be alternatively performed. Venous cannulation can either be peripheral, surgical or percutaneous, or through the right atrial appendage. Myocardial protection is accomplished through the root or directly into the coronary ostia in case of more than moderate regurgitation or when additional doses have to be repeated. Retrograde cardioplegia can be administered either directly into the coronary sinus or peripherally via internal jugular vein if required. The left ventricle can be vented directly through the aortic valve using cardiotomy suction, a vent placed through the right superior pulmonary vein or indirectly with a percutaneously placed pulmonary artery vent. A transverse aortotomy is placed higher to facilitate its closure and visualization at the end of operation. Retraction sutures, if required, are placed on the edges of the aortotomy, and/or at the commissures to elevate the aortic valve into the center of the operative field. The remaining steps of the procedure are similar to conventional valve replacement. Placement of the aortic valve sutures is facilitated by instruments with long handles. Using a knotting device, such as CoreKnot®, reduces not only valve implant time but guarantees a homogenous distribution of forces between native annulus and sewing ring and avoids breakage of sutures, that in limited access space can be challenging to be replaced.

A number of retrospective studies and several reviews have shown that ministernotomy can be performed safely without the risk of death or other major complications [10–13]. In a meta-analysis of 4586 patients, Brown et al. demonstrated that MIAVR through ministernotomy was associated with shorter ventilation time, intensive care unit (ICU) stay and hospital stay as well as less blood loss within 24 h compared with conventional surgery, although patients undergoing ministernotomy had longer cross clamp and CPB time [9]. No difference was found in terms of postoperative atrial fibrillation, stroke and sternal complications [9]. Similar results were reported by others [11–13]. A meta-analysis of randomized trials showed that ministernotomy significantly reduces the length of stay in the cardiac ICU [12]. Other short term benefits were deduction in blood loss and length of hospital stay [12]. Finally, in a meta-analysis of 4667 patients undergoing MIAVR through any approach, Murtuza et al. reported marginal benefits in perioperative mortality (odds ratio, 0.72; 95% confidence interval, 0.51–1.00; $p = 0.05$), intensive care unit stay, total hospital stay, and ventilation time in the MIAVR group compared to conventional AVR group, although cross clamp, CPB, and total operation times were longer [9].

Data reported in these studies have focused mainly on upper ministernotomy; few studies have described the potential advantages of MIAVR using a right anterior minithoracotomy approach [11, 14–16].

Right anterior minithoracotomy avoids sternal sawing and is associated with a limited skin incision. However, the operative field is smaller and the aortic valve sits deeper within the wound. Exposure can be quite challenging and enhanced by strategic placement of pericardial sutures and, if still limited, by preferentially cannulating peripherally for CPB. This approach is typically performed with a 4–6 cm incision through the second or third intercostal space. Upon entering the pleural space, the right mammary vessels are usually ligated and divided. Some surgeons prefer to dislocate the third or fourth rib from the sternum to enhance exposure with the goal of visualizing the tip of the right atrial appendage. A soft tissue retractor is inserted into the wound followed by a rigid retractor with narrow blades. Cannulation for CPB can be central, requiring advanced technical skills for placing purse strings in the distal ascending aorta and introducing low profile arterial cannulas or can be peripheral, which is the preferential choice in case of difficult exposure and thin or short aorta. Venous cannulation can be either surgically performed or through percutaneous puncture advanced under echo guidance up to the superior vena cava. The cross clamp is applied directly through the incision or from an alternative port. Myocardial protection with antegrade cardioplegia is delivered through the root or directly into the coronary ostia. Retrograde cardioplegia could be also delivered peripherally through percutaneous jugular vein catheter into the coronary sinus. Bloodless field is important and can be obtained by venting left ventricle, same as in ministernotomy approach, through the pulmonary vein or by cardiotomy suction directly through the aortic valve. Technical details of aortotomy, prosthetic valve implantation and aortotomy closure are identical to ministernotomy approach. The aortic valve is excised in the usual fashion; however, valvectomy and decalcification should be carefully carried out because management of annular damage or tears can be challenging through minimal access.

Pacemaker wires should be placed before declamping. Central aortic cannula has to be removed first with low arterial pressure and patient can be filled from the femoral venous line. Protamine can be administered once any bleeding issue is resolved; in case of percutaneous femoral venous cannulation the cannula can be re-sheathed during heparin reversal and removed later with simple groin compression.

At the end of the procedure, a small chest drainage tube (e.g. 19 or 24 Fr Blake) is inserted in the right pleural cavity through a separate intercostal space. Pericardium is normally left open or partially closed. The disarticulated rib is reattached to the sternum using non-absorbable, braided suture. To avoid lung herniation, the ribs are then reapproximated using further non-absorbable braided sutures.

In 2011, we reported our first experience with MIAVR using a right anterior minithoracotomy approach and showed excellent surgical results in terms of mortality, morbidity, and patient satisfaction [13]. Contrary to the ministernotomy approach, all patients scheduled for right anterior minithoracotomy should undergo CT scan without contrast enhancement to evaluate the anatomic relationship between the intercostal spaces, ascending aorta, and aortic valve. Patients are suitable for the right anterior minithoracotomy only if the following criteria are met: (1) at the level of main pulmonary artery, the ascending aorta is rightward (more than one half located on the right with respect to the right sternal border); (2) the distance from the ascending aorta to the sternum does not exceed 10 cm; (3) the α angle (angle between the midline and the inclination of ascending aorta) should be >45° (Fig. 46.2). Major exclusion criteria for the right anterior minithoracotomy approach are ascending aortic and/or root dilatation that requires treatment, while minor exclusion criteria are previous cardiac surgery and history of right-sided pleuritis or severe lung emphysema [13].

From January 2005 and June 2010, 192 consecutive patients underwent isolated MIAVR through right anterior minithoracotomy [13]. Overall mortality was 1.6% and the rate of intraoperative conversion was 1.6%. Interestingly, although the cross clam and CPB time were longer than in the standard approach, the incidence of postoperative atrial fibrillation and blood transfusion were 18% and 16%, respectively. The median length of stay was 5 days and discharge home was 90%. Finally, 96% of patients believed they had an aesthetically pleasing scar and 95% were back to their normal activities within 4 weeks. The potential advantages of right anterior minithoracotomy approach were demonstrated in comparison to conventional surgery in a propensity matched study [17]. Specifically, 138 patients undergoing right anterior minithoracotomy were matched to a full sternotomy group using propensity score analysis. The overall in-hospital mortality was 0.7%, with no difference between the two groups. MIAVR via right anterior minithoracotomy was associated with a lower incidence of postoperative atrial fibrillation (18.1% vs. 29.7%) and blood transfusions (18.8% vs. 34.1%) compared to full sternotomy. In addition, patients in the right anterior minithoracotomy group had a shorter mechanical ventilation time (6 vs. 8 h) and postoperative length of stay (5 vs. 6 days). No difference was found in terms of late mortality at median follow-up of 30 months (range, 17–54 months). Finally, among patients undergoing MIAVR, we found that patients receiving right anterior minithoracotomy had better outcomes than those receiving ministernotomy in terms of lower postoperative atrial fibrillation (19.5% vs. 34.2%), shorter ventilation time (median 7 vs. 8 h) and hospital stay (median 5 vs. 6 days) [18]. Interestingly, in all our studies, we always found a low rate of atrial fibrillation associated to right anterior minithoracotomy approach. This might be related to reduced trauma induced by the right anterior minithoracotomy, to the preservation of the sternum which reduces postoperative pain and improves respiratory function, to the smaller pericardial incision and the absence of manipulation of the right atrium for the venous drainage which reduces the inflammatory response, triggering less atrial fibrillation. Therefore, the shorter ventilation time, the less loss blood as well as the low rate of atrial fibrillation and blood transfusions, translate in shorter hospital stay, faster recovery and reduced utilization of rehabilitation resources [18].

Criticism

Over the past two decades MIAVS has been gradually introduced into clinical practice. The increasing popularity of less invasive procedures allows surgeons to perform complex cardiac interventions with the same quality even through smaller incisions. Overall, minimally invasive surgery and combined procedures or staged/hybrid procedures are associated with good outcomes, even in high-risk populations.

Although MIAVR has showed excellent results, there are still criticisms of this approach. Firstly, there is a perception that MIAVR is more to do with cosmetic results rather than better clinical outcomes, as the majority of published studied are retrospective and randomized trials have not showed any potential advantages [10–13]. However, these randomized trials are underpowered and out dated. We are convinced that in the current era, it will be very difficult to design a prospective randomized trial as MIAVR is already showing equivalent results compared to full sternotomy and patients now preferentially demand less invasive procedures.

The second criticism is related to the morbidity due to peripheral cannulation causing wound infection, pseudoaneurysm and neurological events. In order to avoid these complications, our preference is to cannulate the ascending aorta, which allows a more direct and physiological flow. We have recently demonstrated that retrograde perfusion is an independent risk factor for neurological complications such as stroke and postoperative delirium [19].

Third criticism pertains to the costs of minimally invasive surgical instruments and devices. Although all the instruments and devices used for MIAVR are more expensive, we strongly believe that these costs are offset against less rate of postoperative complications, shorter hospital stay and faster recovery all of which translate into less resource utilization and therefore lower overall costs. However, this hypothesis needs to be evaluated with a well-designed cost-analysis study.

Fourth, minimally invasive surgery is not "surgeon friendly' as it is more complex and technically demanding. It entails a distinct learning curve because of the depth of the operative field, the limited exposure and cramped working space for implantation of the prosthetic valve as well as the use of new equipment and methods [20]. With regard to this problem, we have evaluated a single surgeon's learning curve (M.G.) with right anterior mintithoracotomy using the cumulative sum (CUSUM) analysis [21]. Surgical failure was defined as the occurrence of one or more of the following events: perioperative death, intraoperative conversion to full sternotomy, perioperative myocardial infarction, arrhythmias, postoperative complete atrioventricular block, acute renal failure, neurological events, reoperation for bleeding, prolonged ventilation time and surgical wound infection. Analysis of the first 100 cases showed that there was a low risk of cumulative failures from the outset, and no learning curve effect was observed. Therefore, patients undergoing MIAVR through right anterior minithoracotomy are not exposed to an increased operative risk during the surgeon's initial experience. However, we strictly recommend following our CT scan rules and selection of low risk patients at the start of the experience. Once surgeon feels confident with this new technique, he should select higher risk patients, who will have the greater benefit.

Finally, MIAVR is associated with longer CPB and cross clamp times, and this has raised some concerns regarding its safety in elderly and high risk patients. This is mainly because prolonged CPB and cross clamp times are well known risk factors for adverse outcomes after cardiac surgery [22, 23]. Despite our studies show excellent results, we can confirm that patients undergoing MIAVR via right anterior minithoracotomy had longer operative times than those who received a full sternotomy [14, 17, 18]. This is a limitation of MIAVR, suggesting that limited exposure makes implantation of the prosthetic valves more challenging than the conventional approach. However, the use of the sutureless valves has reduced the operative times, further facilitating and standardizing MIAVR.

MIAVR with Sutureless Valves

In recent years, three different sutureless or rapid deployment aortic valves have been introduced in Europe for use in both conventional AVR and MIAVR operations—the ENABLE™ Valve System (Medtronic), the PERCEVAL S™ Valve System (Livanova), and the EDWARDS INTUITY™ Valve System (Edwards Lifescience) (Fig. 46.3). Favourable clinical outcomes with the use of these valves have been reported in several studies [24–26]. However, relatively few studies report clinical outcome of patients who underwent MIAVR using sutureless valves. To date, we have published the largest case series of patients who underwent MIAVR through right anterior minithoracotomy and ministernotomy, reporting excellent hemodynamic results, postoperative outcomes, and short postoperative operative times [27]. Specifically, our operative mortality was 0.7% and compared well with our previous studies of MIAVR with stented valves. We found a 38% and 40% reduction in the cross clamp and CPB time in the right anterior thoracotomy group and 43% and 35% in the ministernotomy group, confirming that sutureless valves can facilitate and standardize the surgical procedure. In addition, we found a very low incidence of paravalvular leakage (1.8%), a frequent complication of TAVI procedure. It has been shown that significant paravalvular leakage is associated with higher risk of late mortality [28, 29]. To avoid paravalvular leakage while implanting sutureless valves, we strongly recommend a thorough decalcification of the aortic annulus. In our experience, this has reduced dramatically the number of paravalvular leakages in our first series [27]. In a recent study of patients undergoing sutureless valve implantation via ministernotomy, Santarpino et al. showed better

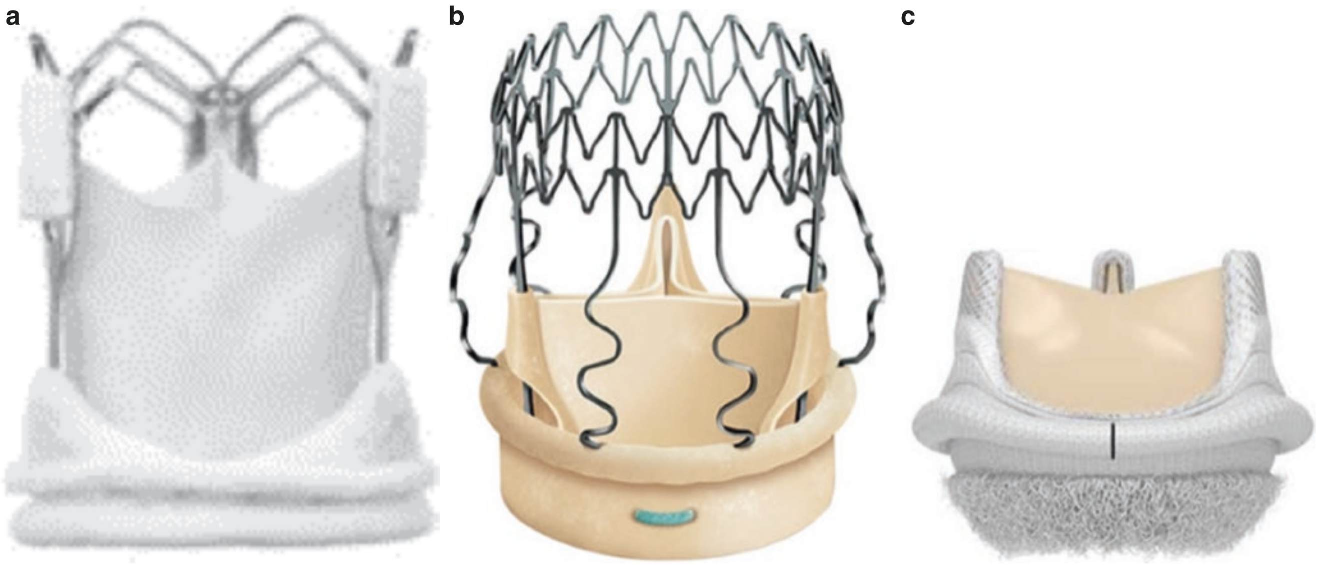

Fig. 46.3 Sutureless and rapid deployment valves. (**a**) Enable™; (**b**) Perceval S™; (**c**) Intuity™

outcomes, suggesting that the combination of a minimally invasive approach with a sutureless valve may be the first-line treatment for high risk patients considered in the gray zone between TAVI and conventional surgery [30, 31].

TAVI has shown excellent results when compared to standard therapy [32]. However, controversies exist when compared to a surgical population [28, 33, 34]. Several studies have concluded that TAVI is ineffective in reducing early and midterm all-cause mortality versus surgical AVR [17, 33]. In addition, transcatheter procedures are associated with greater incidence of neurological events and paravalvular leakages, which are well known risk factors for worse survival [34]. Furthermore, cost analysis studies of TAVI conclude that it is inappropriate to consider reimbursement of TAVI for high-risk operable patients due to the similar mortality rate at 1 year and the higher proportion of postoperative complications associated with TAVI [35, 36]. However, these studies focused on a group of patients undergoing conventional surgery with stented-sutured valves. Therefore, in the light of good hemodynamic performance of sutureless valves, the low rate of postoperative complications and paravalvular leakages, we believe that the association of MIAVR and sutureless valves may be a valid alternative to the expanding use of TAVI technology.

Conclusions

MIAVS is safe and reproducible. The rate of complications can be minimized with better case selection and appropriate preoperative planning and investigations. Although, cross clamp and CPB times are longer than conventional surgery, the use of sutureless or fast deployment valves may increase the uptake of MIAVR among surgeons. With the introduction of sutureless valves, the operative mortality of MIAVR patients has decreased from 1.6% to 0.7% in a 7 year period [14, 27]. In the light of these results, we believe that MIAVR with a sutureless prosthesis may be considered an "alternative" to TAVI procedure for high-risk "operable patients". However, a randomized trial is required to confirm our hypothesis.

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47

Minimally Invasive Mitral Valve Surgery

Mateo Marin-Cuartas and Piroze M. Davierwala

High Yield Facts
- In 1996 Carpentier performed the first video-endoscopic minimally invasive mitral valve (MV) repair through a right minithoracotomy.
- Short- and long-term mortality following MV repair procedures is similar for a conventional sternotomy and a minimally invasive approach.
- Large series have demonstrated that 30-day mortality for both accesses ranges between 0.2% and 2.6%.
- Long-term survival following minimally invasive MV repair is comparable to that achieved with conventional MV surgery.
- Groin seroma and superficial infection are the most commonly reported complications, occurring in 1–7% of patients.
- Stroke occurs in 1–2.6% of patients undergoing minimal invasive MV surgery.
- Conversion of a right mini-thoracotomy to a median sternotomy (most commonly for bleeding) occurs in 0–3.9% of patients.

Introduction

Minimally invasive mitral valve (MV) procedures are being performed by an increasing number of surgeons over the last 15–20 years. This alternative approach for MV surgery offers similar efficacy and safety to that achieved through a standard median sternotomy, particularly in high-volume centers, as evidenced by low perioperative morbidity and mortality rates [1]. Moreover, patient approval of surgical treatment of MV disease is greater due to shorter recovery times, lesser restriction of activities and superior cosmetic results. However, these techniques are technically more challenging and associated with a significant learning curve. Therefore, a large variability exists in the adoption rates of minimally invasive operations ranging from less than 30% in the USA to nearly 50% in Germany [2–4]. The current guidelines recommend surgical intervention even for patients with asymptomatic mitral regurgitation (MR) in centers of experience, where the mortality risk is lower than 1% and the likelihood of repair is greater than 90% [5, 6]. Similar standards are also expected from minimally invasive mitral repair procedures, making it an attractive but challenging surgical alternative, which requires greater surgical dexterity and experience. This chapter offers an overview of the most relevant aspects related to minimally invasive MV surgery with direct visualization or thoracoscopic assistance. Although robotic cardiac surgery is the least invasive technique of performing minimally invasive surgery, its technical complexity and distinct instrumentation deserves a detailed discussion, which is beyond the scope of this chapter.

Brief History

MV repair is being performed for decades. The first attempts at MV repair were about a century ago [7, 8]. However, Carpentier's landmark paper entitled "The French Correction" [2] published in 1983 standardized and facilitated the modern era of MV repair. Introduction of modified cardiopulmonary bypass (CPB) circuits and techniques as well as long-shafted surgical instruments enabled the performance of safe and efficacious minimally invasive MV surgery [9, 10]. Cohn and Cosgrove among others established modified less invasive sternal incisions for MV surgery [11–13]. In 1996 Carpentier performed the first video-endoscopic minimally invasive MV repair through a right minithoracotomy [3] and in 1998, the first completely robotic MV repair

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Table 47.1 Levels of minimally invasive cardiac surgery[a]

Level 1	Direct vision: (10–15 cm incisions)
Level 2	Direct vision/video assisted with mini incisions (4–6 cm)
Level 3	Video directed and robot assisted with micro incisions (1.5–4 cm)
Level 4	Robotic (computer telemanipulation) and totally endoscopic port incisions (<1.5 cm)

[a]Modified from Ref. [1]

using robotic telemanipulation with the da Vinci Surgical System (Intuitive Surgical, Sunnyvale, CA) [4]. Mohr and colleagues introduced the voice-controlled robotic camera in 1998 [5] and subsequently instituted large scale thoracoscopic minimal invasive and robotic MV repair programs with excellent results [14–17].

Definition

The term "minimally invasive MV surgery" has been traditionally defined as a small chest wall incision that does not involve a full sternotomy [6]. Moreover, the current trend and actual purpose of minimally invasive surgery is avoidance of any kind of sternotomy, a decline in blood product usage, shortening of ventilation times, and intensive care and hospital stays, and reduction in postoperative pain [18]. There are four levels of invasiveness that exist in minimally invasive cardiac surgery (Table 47.1) [19, 20].

The most commonly used minimally invasive approach to the MV is a right mini-thoracotomy. Many other incisions such as lower mini-sternotomy and parasternal incisions have also been described. A special set of surgical instruments are required for these techniques. Visualization is usually enhanced with port-access two-dimensional (2D) or three-dimensional (3D) thoracoscopic cameras.

Patient Selection

Minimally invasive MV surgery via a right mini-thoracotomy can be performed in the vast majority of patients, who require MV repair or replacement. Patients requiring ablation surgery for atrial fibrillation or other right-sided procedures such as tricuspid valve surgery, atrial septal defect closure, heart tumor resection can also be operated using this approach. However, other concomitant procedures such as coronary artery bypass surgery, aortic valve or ascending aorta replacement most commonly require a median sternotomy approach. The absolute and relative contraindications for minimally invasive mitral valve surgery through a right thoracotomy have been summarised in Table 47.2. All types and complexities of MV repairs can be performed through a right mini-thoracotomy. However, the level of complexity of MV repair that can be performed through this approach depends on the expertise and experience of the operating surgeon. Complications, which are inherent to any surgery, do occur during this operation especially during the learning curve of the surgeon and his team. They do reduce with increasing experience provided an optimal procedure rate of at least one to two procedures per week is performed by the team [7]. Outcomes for complex MV disease in experienced hands are comparable to the results achieved via conventional median sternotomy [21–24].

Table 47.2 Contraindications for minimally invasive mitral valve surgery[a]

Absolute
Previous right thoracotomy
Mitral annular calcification
Moderate or severe aortic valve regurgitation
Coronary artery disease requiring CABG
Relative
Calcification of the aortic root/ascending aorta
Severe generalized peripheral arterial disease
Significant aortic root/ascending aortic dilatation
Fixed pulmonary hypertension (>60 mmHg)
Severe pulmonary dysfunction
Right ventricular dysfunction
Symptomatic cerebrovascular disease or recent stroke
Severe liver dysfunction
Significant bleeding disorder

CABG coronary artery bypass grafting
[a]Modified from Ref. [1]

High-risk patients such as those requiring reoperations [24–27], elderly [28, 29] and obese patients [30, 31] and those presenting with MV endocarditis, however, without large peri-annular abscesses [8] may also benefit from less invasive MV surgery.

Preoperative Screening

All candidates for minimally invasive MV surgery require a detailed transthoracic echocardiogram for evaluation of left and right ventricular function, valve pathology as well as the presence and grade of pulmonary hypertension. If the latter is severe, right heart catheterization may be considered. For complex valve pathology, a 2D and 3D transesophageal echocardiogram is recommended for a better planning of repair. Routine lung function tests and standard chest X-ray should also be performed before surgery. A computed tomogram (CT) of the thoracic cage is not routinely required. However, it is strongly recommended in patients with significant chest deformities, those requiring reoperations and in patients who have received prior radiation to assess the density and extent of adhesions. Additionally, surgeons do have the luxury of planning minimally invasive surgery with preoperatively acquired 3D CT reconstruction models that are commonly available nowadays. This imaging modality is a useful and feasible method of determining the operative strategy and excluding patients unsuitable for a minimally invasive approach, thus preventing potential complications [32].

Screening for coronary artery disease is not required in patients under 40 years of age as long as they do not have any predisposing risk factors. Patients older than 40 years of age may be screened with CT coronary angiography. Patients older than 60 years or younger patients with cardiovascular risk factors should undergo a preoperative coronary angiogram. All patients undergoing minimally invasive MV surgery undergo a Doppler examination of the carotid arteries. In case of suspected carotid artery disease, carotid CT studies should be performed. Patients with confirmed peripheral artery disease or with risk factors for the same should also undergo tomographic or ultrasound imaging for aortoiliac disease. Femoral artery, as a cannulation site, and aortic endo-aortic balloon occlusion should be avoided in patients with severe aortic atherosclerosis or a dilated ascending aorta. In such cases, the right axillary artery is the optimal site for arterial cannulation. In case of ascending aortic atherosclerosis or severe periaortic adhesions in reoperations direct aortic cross-clamping may not be possible. Surgery should be performed under hypothermic (30 °C) ventricular fibrillation, which is a good alternative strategy.

Operative Management

Surgical Setup

A wide variety of incisions such as partial sternotomy, parasternal, and mini-thoracotomy incisions have been described to access the heart valves. Our standard approach is a right mini-thoracotomy, usually through the fourth intercostal space (ICS), with 2D or 3D video-assistance [1, 22]. The patient is intubated with a single lumen endotracheal tube and given a 30° left lateral position with the right arm positioned posteriorly (Fig. 47.1). CPB is established by cannulation of the femoral artery and vein through a 2–3 cm oblique incision in the groin. The arterial cannula is then fixed to the skin to avoid displacement. Transesophageal echocardiography (TEE) is used to confirm that the tip of the multiport venous cannula is positioned in the superior vena cava. For patients weighing more than 100 kg or those requiring right-sided procedures, a second venous cannula is inserted by the anesthesiologists via the right internal jugular vein. For concomitant right-sided procedures and atrial fibrillation ablation, temporary occlusion of superior and inferior vena cava is accomplished with tourniquets or large bulldog clamps [33, 34].

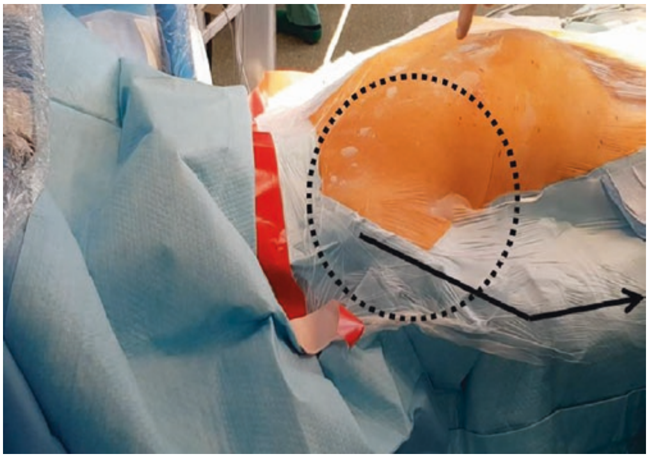

Fig. 47.1 Patient position: 30° left lateral position. The axilla (*black hatched circle*) is completely accessible. The right arm (*black arrow*) lies downwards and outwards

Body temperature is maintained at 34 °C and vacuum-assisted venous drainage is used throughout the procedure. A 5–6 cm right lateral mini-thoracotomy incision is made just inferolateral to the nipple in men and in the submammary crease in women. The thorax is entered through the fourth ICS.

A dedicated instrument set designed for minimally invasive surgery is used to perform the operation. A soft tissue retractor with or without a small thoracic retractor is utilized to spread the ribs. The pericardium is opened 3–4 cm anterior and parallel to the right phrenic nerve, extending from the distal ascending aorta to the diaphragm. A thoracoscope and a transthoracic Chitwood aortic cross-clamp are inserted via the second and third right ICS, respectively (Fig. 47.2). Antegrade crystalloid cardioplegia is delivered directly into the aortic root through a long cardioplegia needle, allowing up to 90–120 min of safe ischemic time. A left atriotomy is performed through a paraseptal incision (Sondergaard groove). Thereafter, standard MV replacement or repair techniques are used, as described below.

Once MV repair has been accomplished, water sealing probe test is used to confirm MV competence (Fig. 47.3). Thereafter, the left atrium is closed and de-aired. The patient is temporarily weaned from CPB to assess the quality of the MV repair and to look for new regional wall motion abnormalities caused by injury/occlusion of circumflex artery. CPB is then resumed, the cardioplegia needle vent is removed, haemostasis is ensured, and the pericardium is closed. CPB is then weaned off, protamine is administered, and the patient is decannulated. The chest is then closed (Fig. 47.4). All patients undergo transthoracic echocardiography before discharge from hospital and lifelong annual echocardiographic surveillance is recommended as for all MV repair operations [35, 36].

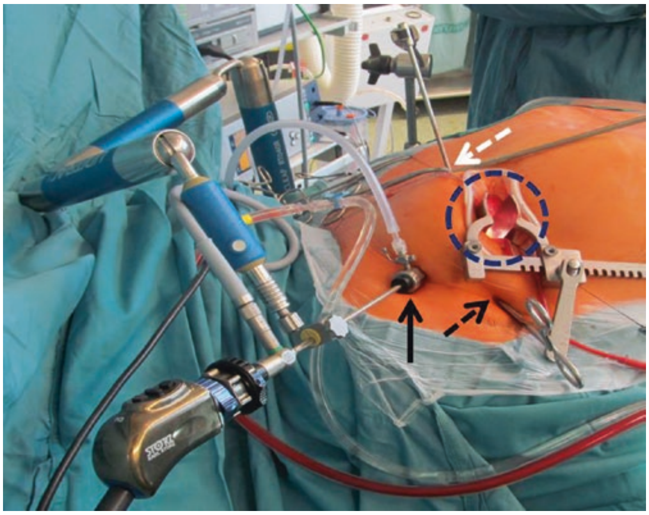

Fig. 47.2 The set-up shows the incision (*blue hatched circle*), the thoracoscope port (*black arrow*), the entry site of the transthoracic aortic clamp (*black hatched arrow*) and the entry site of the left atrial retractor (*white hatched arrow*)

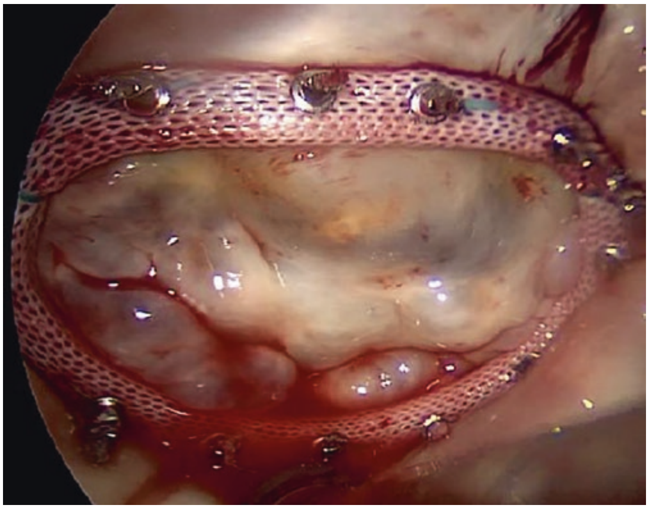

Fig. 47.3 The water test. The line of coaptation should be parallel to the posterior mitral annulus

MV Repair Techniques

Our philosophy for MV repair of myxomatous disease has been "*respect rather than resect*".

Triangular Resection

This technique is ideal for patients with posterior mitral leaflet (PML) prolapse. The extent of leaflet resection is identified by finding normal chordae on either side of the prolapsing portion. A triangular-shaped segment of tissue is excised with a curved scissor. Continuous or interrupted 4-0 polypropylene suture is used to close the defect in the leaflet.

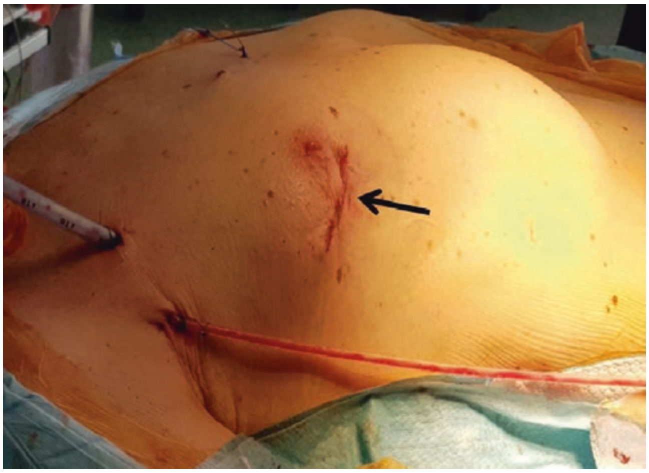

Fig. 47.4 The closed incision (*black arrow*) with two chest drains

Quadrangular Resection with Sliding Plasty

This technique is employed in patients with markedly elongated leaflets and redundant tissue (Barlow's disease) inducing an extensive, redundant PML prolapse. The prolapsing, excessively tall segment of posterior leaflet is excised and then the remaining portions of the PML are detached from the annulus and advanced centrally, "sliding" them over, to meet one another. The lateral and medial PML segments are reapproximated and the base of the PML is reattached to the annulus with a continuous 4-0 polypropylene suture.

Neochordae Implantation

Leaflet prolapse (Fig. 47.5a) is corrected by inserting artificial chordae made of polytetrafluorethylene (PTFE) sutures between the papillary muscle and the leaflet segments that have elongated or ruptured chordae tendinae. For minimally invasive MV surgery, PTFE neochordae placement is facilitated by the "Leipzig Loop technique" [9]. Correct length of the PTFE loops is determined using a caliper (Fig. 47.5b), and the loops are then attached to the papillary muscle (Fig. 47.5c) and to the free edge of the prolapsing segment(s) (Fig. 47.5d). This technique can be used for both anterior mitral leaflet (AML) and PML prolapse.

Alfieri Stitch

The figure of eight edge-to-edge Alfieri's stitch (Fig. 47.6) may be performed in the elderly or significantly morbid patients, in whom reduced operative times are important. This technique is also recommended in pathologies with a high probability of development of systolic anterior motion (SAM) following repair. Commisural prolapse can be easily corrected with this stitch.

Annuloplasty

All repairs are supported by insertion of an annuloplasty ring (usually complete and semi-rigid) or band. Functional MR is

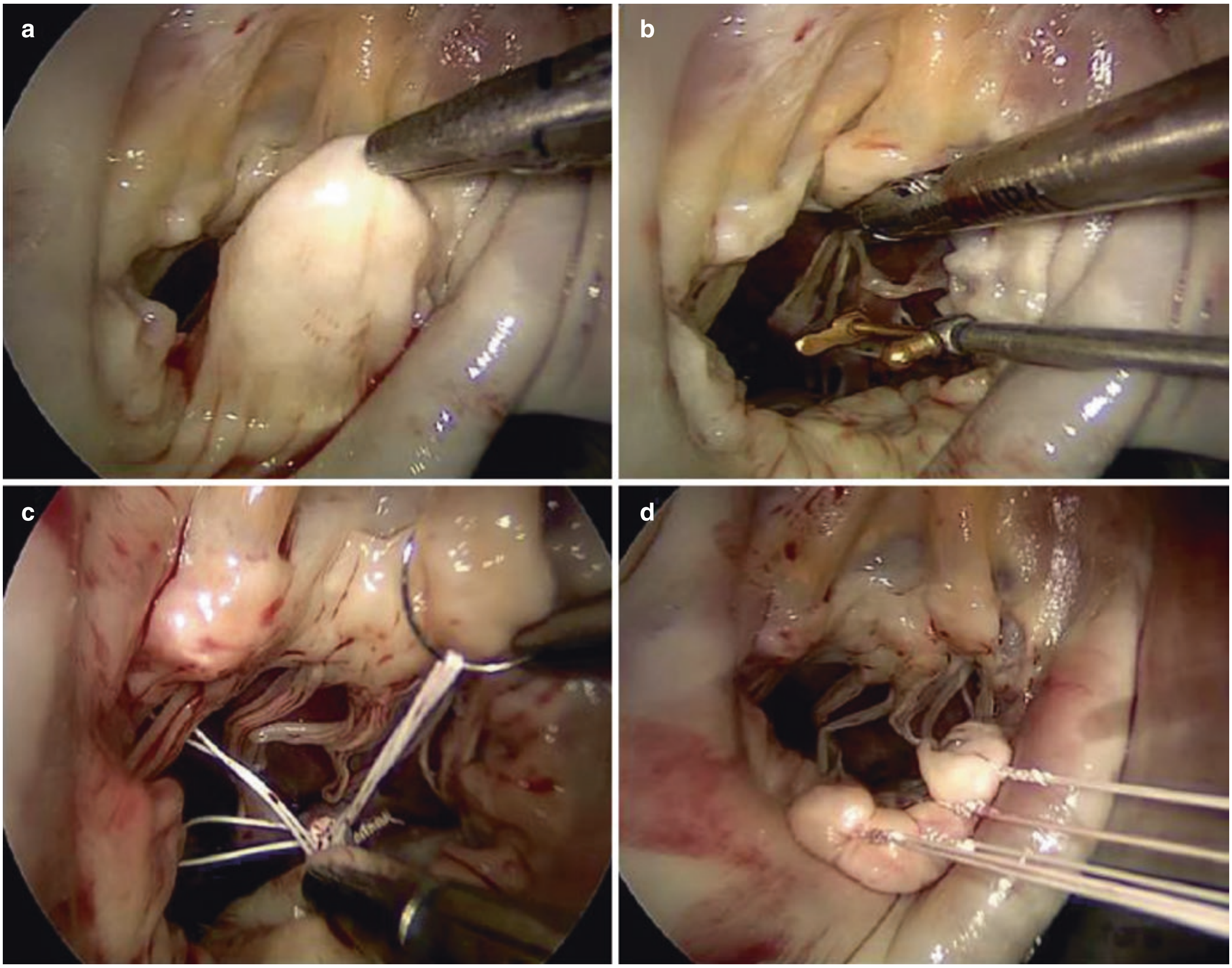

Fig. 47.5 (**a**) P_2 prolapse. (**b**) Measurement of length of loops. (**c**) Loops attached to the postero-medial papillary muscle. (**d**) Loops attached to the free margin of P_2

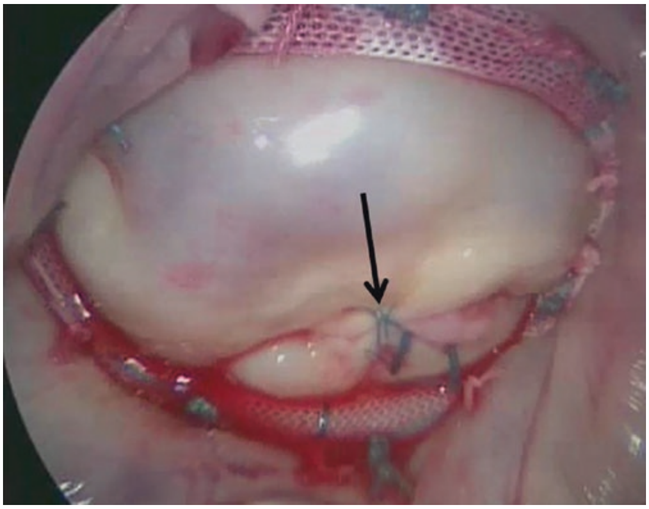

Fig. 47.6 Alfieri Stitch (*black arrow*) for repair of a severely myxomatous bileaflet mitral valve prolapse (Barlow)

repaired by means of a downsized, complete, rigid annuloplasty ring with or without subvalvular procedures.

Short- and Long-Term Results

Short- and long-term mortality following MV repair procedures is similar for a conventional sternotomy and a minimally invasive approach. However, this finding is based on retrospective observational studies, since no well-powered randomized controlled studies comparing both approaches exist in literature. Large series have demonstrated that 30-day mortality for both accesses ranges between 0.2 and 2.6% [22, 37–39]. Similar studies have also demonstrated that long-term survival following minimally invasive MV repair is comparable to that achieved with conventional MV surgery [40, 41]. Our previously published "Leipzig Experience" showed survival rates of 87.0 ± 0.7% at 5 years and

74.2 ± 1.4% at 10 years after minimally invasive MV repair [10]. Furthermore, the rate of repair following a minimally invasive MV repair (>90%) is also similar to that following MV repair through a median sternotomy [22, 38, 39, 42]. Additionally, rates of recurrent MR and need for repeat MV surgery have also been reported to be similar between the two approaches [39, 43]. Our experience showed a freedom from reoperation of 96.6 ± 0.4% and 92.9 ± 0.9% at 5 and 10 years, respectively [10].

Advantages, Disadvantages and Complications

An increasing proportion of patients are requesting minimally invasive surgery because of perceived advantages. Reduction in pain and faster return to normal activity has been demonstrated in several studies [30, 44–46]. Pain may be the same or slightly greater to a full sternotomy approach for the first two postoperative days, with a significant reduction thereafter [11]. Studies have also shown that patients undergoing a minimally invasive approach as a reoperation felt that their recovery was more rapid and less painful than after their previous sternotomy procedure [47, 48]. Other reported benefits of a minimal invasive approach include less bleeding (although without a reduction in rates of re-exploration for bleeding), decreased ventilation times, reduced atrial fibrillation, decreased wound infections, and shorter hospital stays [21, 30, 41, 44, 46–52].

There are, however, drawbacks associated with a minimal invasive approach to the MV. Myocardial ischemic and CPB times are longer than those during a conventional median sternotomy approach, due to increased technical demands of working through a confined space [12]. In high volume centers, however, operating times approach those achieved with a conventional approach [13].

One meta-analysis reported that stroke rates may be increased with a minimally invasive approach [14], presumably because of retrograde perfusion of the aorta during CPB or balloon migration during endoaortic clamping. This dreaded complication occurs in 1–2.6% of patients undergoing minimal invasive MV surgery [22, 39]. In a more recently published meta-analysis, however, minimal invasive surgery was no longer associated with an increased risk of stroke [15]. The choice between direct aortic clamping and balloon endoclamping varies from center to center. Similar mortality and stroke rates have been observed using either of the techniques [16].

Another disadvantage associated with minimally invasive surgery is the possibility of complications following peripheral cannulation [17]. Groin seroma and superficial infection are the most commonly reported complications, occurring in 1–7% of patients [53–58]. Leg ischemia during retrograde perfusion is very rarely observed and if seen can be managed by placing a perfusion cannula from the CPB arterial cannula into the distal femoral artery and/or monitoring oxygen saturation on the legs. These measures are, however, not required routinely. Retrograde aortic dissection is a rare but life-threatening complication of peripheral cannulation.

Another infrequent, but potentially life-threatening complication observed with minimal invasive MV surgery is unilateral pulmonary edema [18]. Phrenic nerve injury is another possible complication, which could be a major problem for patients with compromised pulmonary function. It could be avoided by opening the pericardium 3–4 cm anterior to it and by avoiding traction on the lower pericardial edge that may cause diaphragmatic paresis due to stretching of the nerve.

Finally, conversion of a right mini-thoracotomy to a median sternotomy (most commonly for bleeding) is another described complication of minimal invasive MV surgery, occurring in 0–3.9% of patients [22, 38, 39, 53, 59].

The Future

New approaches are constantly being developed in order to minimize the trauma and improve the cosmetic results without compromising the surgical results. A perfect example of this is the periareolar incision, commonly known as the "nipple-cut", which has shown to achieve excellent outcomes in well selected patients [26, 45, 60] (Table 47.3).

Minimally invasive MV surgery should be considered as an opportunity for learning since port-access video-assistance allows excellent visualization of the MV for the entire surgical team. In addition, several simulators exist for practicing manual skills and familiarizing oneself with long instruments required to perform these techniques.

Although these techniques are well established in referral centers, future innovations should concentrate on decreasing complexity and improving reproducibility of these procedures in low volume centers.

Table 47.3 General considerations for periareolar approach[a]

Gender	Feasible for both genders
Areolar diameter	At least 3 cm
Incision	Should not extend over 180°
Obese patients	Not contraindicated. Breast flattens around the areolar region after patient is positioned on the surgical table
Breast implants	Not contraindicated. The breast implants can be explanted and kept in saline solution with antibiotics during the procedure
Contraindications	History of breast irradiation or surgery for cancer with reconstructive breast surgery (mastopexy)

[a] Modified from Refs. [26, 45, 60]

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Transcatheter Aortic Valve Therapies

48

Mohanad Hamandi and Michael J. Mack

High Yield Facts

- In 2002, Cribier and colleagues implanted the first transcatheter aortic valve.
- Transcatheter aortic valve implantation (TAVI) is an effective treatment option in patients with severe aortic stenosis at intermediate, high, and prohibitive surgical risk.
- PARTNER 1B trial was the first randomized controlled trial that compared TAVI with SAPIEN transcatheter heart valve to medical therapy in 358 patients with prohibitive surgical risk.
- PARTNER 1B trial showed an absolute survival benefit at 1 year with TAVI of 20% (30.7% vs. 49.7%) when compared to standard medical therapy.
- PARTNER 1A trial enrolled 699 patients with severe aortic stenosis who were at high surgical risk and randomized to either surgical aortic valve replacement (SAVR) or transfemoral or transapical TAVI.
- In PARTNER 1A trial TAVI was found to be non-inferior with respect to the primary endpoint, all-cause mortality at 1 year (24.2% in TAVI vs. 26.8% in SAVR).
- PARTNER 2A trial enrolled 2032 patients with severe aortic stenosis who were at intermediate surgical risk.
- PARTNER 2A trial demonstrated TAVI to be non-inferior to SAVR with a primary endpoint of mortality and disabling stroke (19.3% vs. 21.1%) at 2 years.
- Pacemaker rates, stroke, valve durability and thrombosis are challenging issues that need to be addressed before TAVI use in low surgical risk patients.
- The Heart Team is pivotal to determine the optimal treatment for each patient based on the risk evaluations, frailty, comorbidities and patient preference.

Introduction

History of Transcatheter Aortic Valve Implantation (TAVI)

Catheter-based balloon aortic valvuloplasty (BAV) was developed in 1985 to offer a treatment option for inoperable patients with severe aortic stenosis (AS) [1]. However, BAV was limited by the high rate of restenosis that occurred in 80% of patients at 1 year [2]. Transcatheter heart valves (THVs) utilized the combination of stent frame to prevent restenosis and a valvular structure within the stent to replicate native valve function. In 1992, Anderson and colleagues [3], first reported successful implantation of a stented valve in a pig model. The first in human implantation of a transcatheter valve was performed in 2000 by Bonhoeffer and colleagues [4] when they implanted a THV in the pulmonary position in a 12-year-old boy. Cribier began experiments on sheep models to achieve the first implantation of THV within native aortic valve [5]. After more than 100 animal experiments, major improvement in the THV design, appropriate implantation techniques and delivery systems for use in humans were completed [5]. In 2002, Cribier and colleagues implanted the first TAVI in a 57-year-old man with severe AS, cancer and prohibitive risk for surgical aortic valve replacement (SAVR) [6]. Several European clinical studies evaluated the technology and approaches that

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resulted in obtaining CE mark approval in Europe in 2007 and subsequent randomized trials in North America led to US approval in 2011.

The Heart Team Approach

Since the introduction of TAVI, the Heart Team concept has become increasingly utilized in managing patients with cardiovascular diseases. The goal is to offer a complementary approach to patient care by shared decision making among health care providers including cardiac surgery, interventional cardiology and imaging specialists. Given the large amount of new scientific data, the development of new devices, and a patient-centered approach to care, the Heart Team has become of paramount importance in managing patients with severe AS. It has been recommended by multiple specialty societies and is also mandated by the U.S Food and Drug Administration (FDA) and Centers for Medicare and Medicaid Services (CMS) [7].

Risk Assessment

Accurate risk assessment for any medical procedure is a major component of shared decision making and patient informed consent. Current management of patients with AS relies significantly on risk-stratification models derived from the surgically treated population in addition to frailty assessments and clinical judgment. The most widely used are the logistic EuroSCORE, EuroSCORE II and the Society of Thoracic Surgeons Predictive Risk of Mortality (STS-PROM) score which were developed and validated in surgical population. Since the introduction of TAVI, these risk models have been used in the preoperative assessment of patients with severe AS to assess their candidacy for TAVI or SAVR. Several studies have shown the inability of these models to assess procedural risk for TAVI properly [8, 9]. In 2016 the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry (STS/ACC TVT) published a risk score to predict the in-hospital mortality after TAVI. It was developed from the TVT registry which captures all commercial TAVI procedures in the United States. However, it currently predicts only the in-hospital mortality and does not include frailty measures [10].

Latest Generation Transcatheter Valves

SAPIEN 3

The Edwards SAPIEN 3 THV (Edwards Lifesciences, Irvine, CA) is the latest generation of the balloon-expandable SAPIEN valves. It consists of three bovine pericardial leaflets sutured to a cobalt chromium stent frame (Fig. 48.1c). It is designed to improve the outcomes of its predecessors SAPIEN (Fig. 48.1a) and SAPIEN XT (Fig. 48.1b) by adding an outer skirt to decrease the occurrence of paravalvular leakage (PVL) [11]. However, the need for new pacemaker after TAVI with SAPIEN 3 THV was initially higher than reported with previous generations but with modified sizing algorithms this is no longer the case [12]. Major outcomes and valve details are summarized in Table 48.1 from a weighted meta-analysis of 30 studies including 5923 patients from January 2011 to March 2016 [13].

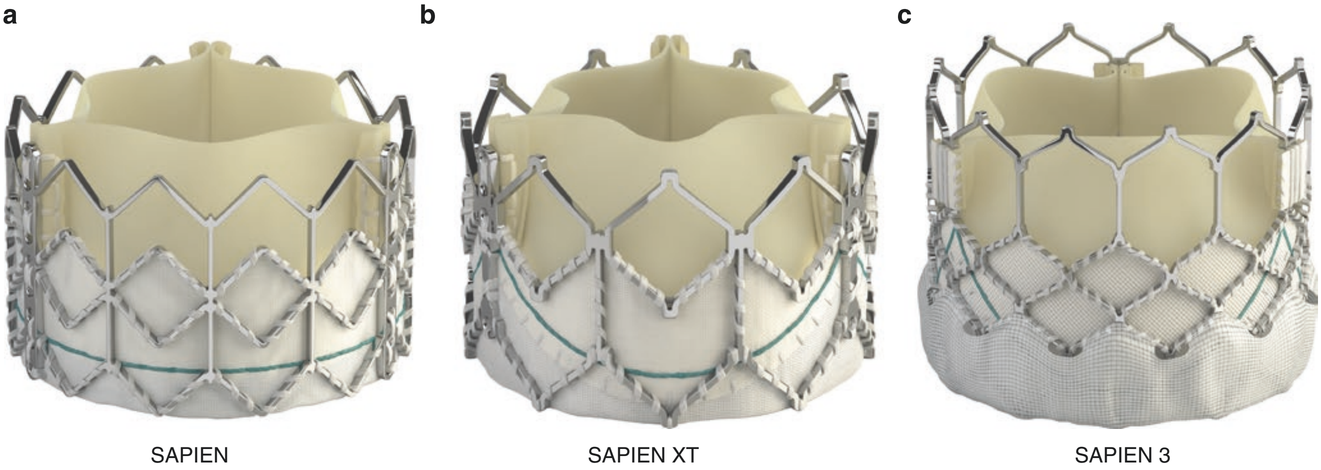
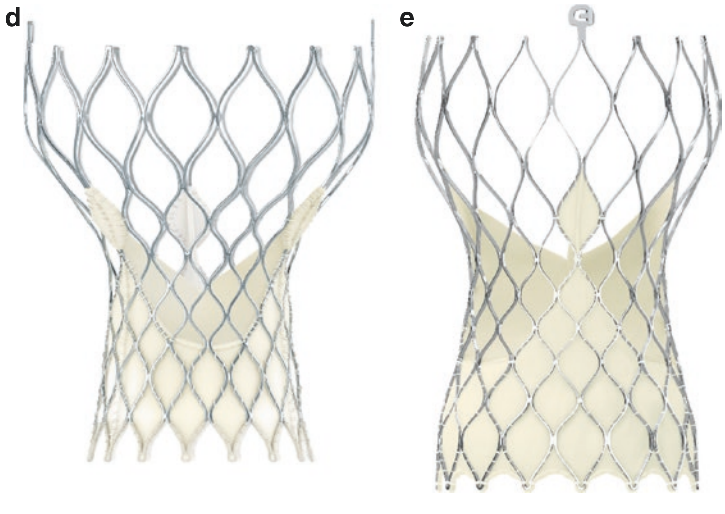


Fig. 48.1 Transcatheter heart valves in the landmark trials. (**a**–**c**) *Adapted with permission from Edwards Lifesciences.* (**d**, **e**) *Adapted with permission from Medtronic*

Fig. 48.1 (continued)



Core Valve Evolut R

Table 48.1 Available transcatheter heart valves

Device	Valve structure	Access route and valve size	Retrievable	30-day mortality	New PPM	Major stroke	Major vascular complications
SAPIEN 3 (Edwards Lifesciences)	BE, bovine tissue valve; cobalt chromium frame	TF, TA, TAo: 20, 23, 26, 29 mm	No	2.3% (CI 95%, 1.2–4.3)	12.4% (CI 95%, 11–14)	1% (CI 95%, 0.6–1.5)	5.3% (CI 95%, 4.4–6.4)
Evolut R (Medtronic)	SE, porcine tissue valve; nitinol frame	TF, TAo, TSc: 23, 26, 29, 34 mm	Yes	2.6% (CI 95%, 1.3–4.9)	15.2% (CI 95%, 10.9–18.8)	3.6% (CI 95%, 1.7–6.5)	5.9% (CI 95%, 1.9–7)
Lotus (Boston Scientific)	ME, bovine tissue valve; nitinol frame	TF: 23, 25, 27 mm	Yes	3.9% (CI 95%, 1.8–8.4)	32.1% (CI 95%, 27.7–36.9)	2.8% (CI 95%, 1.5–5.1)	2.4% (CI 95%, 1.3–4.6)
Portico (St. Jude Medical)	SE, bovine tissue valve; nitinol frame	TF, TAo TSc: 23, 25, 27, 29 mm	Yes	3.4% (CI 95%, 1.4–8.4)	8.9% (CI 95%, 5.1–15.2)	3.4% (CI 95%, 1.4–8.4)	0%
ACURATE Neo (Symetis)	SE, porcine tissue valve; nitinol frame	TF, TA: small, medium, large	No	6.8% (CI 95%, 4.3–10.4)	9.7% (CI 95%, 6.7–13.8)	3.6% (CI 95%, 0.5–21.6)	0%
JenaValve (JenaValve Tech.)	SE, porcine tissue valve; nitinol frame	TA: 23, 25, 27 mm	No	11.2% (CI 95%, 7.9–15.6)	9.6% (CI 95%, 5.8–15.6)	2.4% (CI 95%, 1–5.7)	6.1% (CI 95%, 3.8–9.9)
CENTERA (Edwards Lifesciences)	SE, bovine tissue valve; nitinol frame	TF, TSc: 23, 26, 29 mm	Yes	1%	4.5%	2.5%	6.4%

BE balloon-expandable, *SE* self-expandable, *ME* mechanical-expandable, *TF* transfemoral, *TA* transapical, *Tao* trans-aortic, *TSc* trans-subclavian, *CI* confidence interval, *PPM* permanent pacemaker

Sources: Todaro D, et al. Current TAVR Devices Technical characteristics and evidence to date for FDA- and CE Mark-approved valves. Cardiac Interventions Today, April 2017, Accessed January 2019, URL https://citoday.com/2017/04/current-tavr-devices/

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Evolut R

The Medtronic CoreValve Evolut R THV (Medtronic, Minneapolis, MN) is the latest generation of CoreValve system. It consists of three porcine pericardial leaflets sutured within self-expanding nitinol stent frame (Fig. 48.1e). It is designed with shorter frame height, extended skirt and retrievability compared to the previous generation CoreValve systems (Fig. 48.1d). A large comparison between Evolut R and CoreValve systems showed that patients receiving Evolut R had lower incidence of all-cause mortality, less need for new pacemaker, and less PVL [14].

Table 48.1 provides a summary of FDA and CE Mark approved valves including major outcomes and valve details [13].

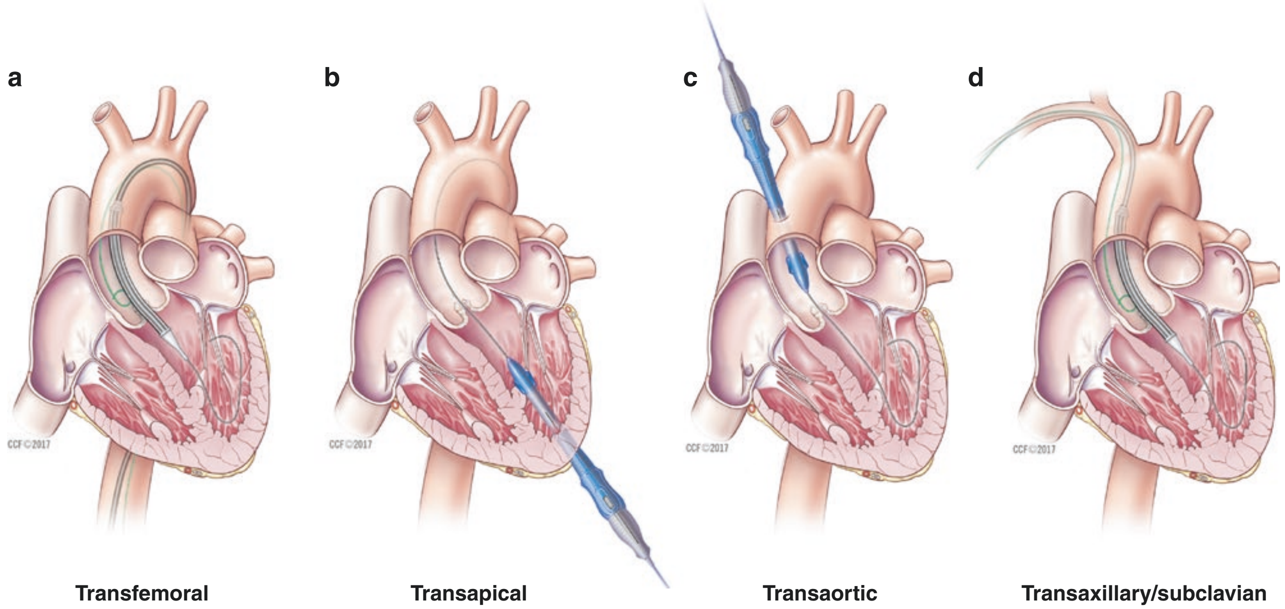

Fig. 48.2 TAVI access routes. (*Reproduced with permission from Cleveland Clinic Foundation*)

Access Routes

In the current practice, TAVI is predominantly performed via transfemoral (TF) arterial approach, which delivers the THV in a retrograde fashion into the native aortic valve annulus (Fig. 48.2). The TF approach was utilized in the early TAVI trials utilizing a 22- or 24-French sheath for SAPIEN THV and an 18-French sheath for CoreValve THV [15–17]. The transapical (TA) approach was the most alternative access of THV delivery [18]. However, in PARTNER 1A (Placement of Aortic Transcatheter Valve) trial the TA approach had higher early mortality as compared to the TF approach and SAVR [16]. With the development of newer generations THV and delivery systems, further alternative access routes have been utilized for selected patients with appropriate anatomy. Transsubclavian, transaortic, transcaval, and transcarotid are currently available in clinical practice [18]. TF access is currently the primary mode of delivery in 95% of patients with the subclavian access approach the most common route in the remainder (Fig. 48.2).

Landmark TAVI Trials

TAVI was evaluated in multiple randomized trials that led to its approval in prohibitive, high and intermediate surgical risk patients. The surgical risk was defined based on STS-PROM and other metrics such as frailty and co-morbidities. The evaluation and determination of the risk category is a Heart Team decision since the multidisciplinary team approach evaluates multiple factors in addition to the risk score in reaching a final treatment decision. The summary of all randomized trials is included in Table 48.2.

Prohibitive Risk

PARTNER 1B [15] trial was the first randomized controlled trial (RCT) that compared TAVI with SAPIEN THV (Fig. 48.1a) to medical therapy in 358 patients. In 2010, the results were published showing an absolute survival benefit at 1 year with TAVI of 20% (30.7% vs. 49.7%) when compared to standard medical therapy. There was also a significant reduction in symptoms and improvement in quality of life. Although there was a higher incidence of major stroke with TAVI (5.0% vs. 1.1%) at 30 days, the improvement in survival and symptoms outweighed the impact of this complication. The US Pivotal trial [17] studied CoreValve (Fig. 48.1d) in inoperable patients with AS, also called “extreme risk”. The study met its primary endpoint of 12-month all-cause mortality or major stroke with a combined incidence of 26% at 1 year. The need for a new permanent pacemaker (PPM) was higher in the US Pivotal trial with the CoreValve vs. the Partner 1B trial (21.6% vs. 3.4% at 30 days). These two studies led to the initial FDA approval of the TF SAPIEN system for inoperable patients in November, 2011 and the CoreValve system in January, 2014 in extreme surgical risk patients.

High Risk

The PARTNER 1A trial [16] enrolled 699 patients with AS who were at high surgical risk. These were randomized to either SAVR or TF or TA TAVI. TAVI was found to be non-inferior with respect to the primary endpoint, all-cause mortality at 1 year (24.2% in TAVI vs. 26.8% in SAVR). The mortality at 30-day and 1-year were similar between both arms, however,

Table 48.2 Summary of the landmark TAVI trials

Trial	Risk	TAVI	Comparator	30-Day mortality	1-Year mortality	Major stroke[a]	New PPM[b]
PARTNER 1B [15]	Inoperable	Balloon-expandable	Medical management/ BAV	5.0 vs. 2.8	30.7 vs. 49.7	5.0 vs. 1.1	3.4 vs. 5.0
CoreValve Pivotal [17]	Inoperable	Self-expandable	Objective performance goal	8.4	24.3	2.3	21.6
PARTNER 1A [16]	High	Balloon-expandable	SAVR	3.4 vs. 6.5	24.2 vs. 26.8	3.8 vs. 2.1	3.8 vs. 3.6
CoreValve High Risk [19]	High	Self-expandable	SAVR	3.3 vs. 4.5	14.2 vs. 19.1	3.9 vs. 3.1	19.8 vs. 7.1
PARTNER 2A [20]	Intermediate	Balloon-expandable	SAVR	3.9 vs. 4.1	12.3 vs. 12.9	3.2 vs. 4.3	8.5 vs. 6.9
SURTAVI [21]	Intermediate	Self-expandable	SAVR	2.2 vs. 1.7	6.7 vs. 6.8	1.2 vs. 2.5	25.9 vs. 6.6
NOTION [22]	Low risk	Self-expandable	SAVR	2.1 vs. 3.7	4.9 vs. 7.5	1.4 vs. 3.0	34.1 vs. 1.6
Low risk trial [23]	Low risk	Self-expandable and Balloon-expandable	SAVR	0 vs. 1.7	N/A	0 vs. 0.6	5.0 vs. 4.5

Values in %

BAV balloon aortic valvuloplasty, *N/A* not available, *SAVR* surgical aortic valve replacement, *TAVI* transcatheter aortic valve implantation

[a] Major or disabling stroke at 30 days

[b] PPM: new permanent pacemaker at 30 days

there were increased vascular complications and stroke in the TAVI arm. The United States CoreValve High risk study [19] examined the self-expandable prosthesis in high surgical risk patients with severe AS. Similar to the PARTNER 1A trial, high surgical risk patients were randomized to either SAVR or TAVI. The results suggested superiority of the self-expandable prosthesis over surgery in high surgical risk patients with a lower 1-year mortality rate (14.2% vs. 19.1%; p = 0.04 for superiority). Pacemaker rates were again significantly higher in the self-expandable study as compared to the balloon expandable study at 1 year (22.3% vs. 5.7%). These two studies led to the FDA approval for SAPIEN system in 2012 and CoreValve system in 2014 in in high surgical risk patients with severe AS.

Intermediate Risk

PARTNER 2A trial [20] enrolled 2032 patients with severe AS who were at intermediate surgical risk defined as STS-PROM range of 4–8%. This trial evaluated between 2011 and 2013 the second generation balloon expandable SAPIEN XT (Fig. 48.1b). TAVI was again demonstrated to be non-inferior to SAVR with a primary endpoint of mortality and disabling stroke (19.3% vs. 21.1%) at 2 years. TF TAVI was also found to be superior to SAVR and the rate of stroke was not significantly different between the two groups. During this trial, a later generation of the SAPIEN XT valve, SAPIEN 3 (Fig. 48.1c) was introduced. This was evaluated in a nonrandomized registry in intermediate risk patients which was then propensity score matched to the surgical arm of Partner 2A. This valve was similarly shown to be non-inferior to SAVR in intermediate risk patients. The CoreValve was also studied from 2012 to 2014 in the Surgical or Transcatheter Aortic Valve Replacement in Intermediate Risk Patients (SURTAVI) trial [21]. The trial evaluated the first generation CoreValve and also the second generation device, Evolut R (Fig. 48.1e). The STS-PROM range in this trial was 3–15%. The trial showed similar results to the PARTNER 2A trial, and showed that TAVR with non-inferiority to surgery of the primary endpoint of death or disabling stroke at 2 years. These trials led to the FDA approval of the SAPIEN and CoreValve systems for intermediate risk patients.

Low Risk

NOTION (Nordic Aortic Valve Intervention Trial) [22] was the first trial evaluating TAVI vs. SAVR in the low surgical risk cohort. It was an “all comer” randomized trial and enrolled patients (80% low risk) between 2009 and 2013 utilizing the first generation CoreValve device. The primary endpoint, a composite of all-cause mortality, stroke or myocardial infarction (MI) at 1 year post procedure was similar between the two groups (13.1% vs. 16.3% for TAVI and SAVR respectively). There was no difference between the two groups in mortality at 2 years. The TAVI arm patients required new PPMs, but had also lower life threatening bleeds, acute kidney injury and post procedure atrial fibrillation than surgical patients.

The Low Risk trial was a prospective, non-randomized, multicenter registry of low risk patients with severe AS undergoing TAVI. The primary endpoint was all cause mortality at 30 days with no mortality seen and 0.5% stroke rate and a 5.0% pacemaker rate. However, 14% of patients had evidence of subclinical leaflet thrombosis at 30 days [23].

The PARTNER 3 trial began enrolling patients in 2016, comparing TAVI vs. SAVR in low surgical risk patients with a mean STS-PROM of 1.9%. The primary composite outcome is all-cause mortality, stroke, and re-hospitalization at 1-year with extended follow up to 10 years. Similarly, self-expandable prosthesis in a low risk patient trial started in March 2016. The combined primary endpoint is all-cause mortality and stroke at 2 years. The results of these two trials will be available in early 2019.

TAVI Indications and Guideline Recommendations

For patients with severe symptomatic aortic stenosis in whom TAVI is being considered, evaluation by a Heart Team is recommended by the European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS) as well as the American College of Cardiology (ACC)/Society of Thoracic Surgeons (STS) guidelines (Class IC) (Fig. 48.3). Similarly, both guidelines recommend, more specifically mandate in the U.S, that TAVI should only be performed in centers with both cardiology and cardiac surgery on site (ESC/EACTS Class IC) [24, 25].

Current Challenges

In conjunction with expanding indication in intermediate risk patients and the imminent inclusion of low-risk patients, optimizing TAVI outcomes has been of increased focus in the clinical practice. PPM, stroke, and valve thrombosis are among the most significant complications occurring with TAVI.

Permanent Pacemaker

Since the introduction of TAVI in the randomized trials, the increased need for new PPM remains a problem. The implantation of PPM has been associated with reduced survival, prolonged hospital stay and costs [26, 27]. Preexisting right bundle branch block, the prosthesis to left ventricular outflow tract ratio, and landing zone calcifications are some of the identified predictors of a PPM after TAVI [27, 28]. The choice of the THV also plays a role. Table 48.1 summarizes the available THV with their estimated PPM rates. With the expansion towards the low-risk patients, understanding the predictors and clinical implications is of paramount importance to mitigate the need for a new PPM.

Stroke

Cerebrovascular events remain a major TAVI complication that may have a significant impact on a patient's quality of life, morbidity and mortality. Despite the trend towards decreased stroke rates in the recent trials, they can be as high as 15% according American Heart Association/American Stroke Association guidelines [29].

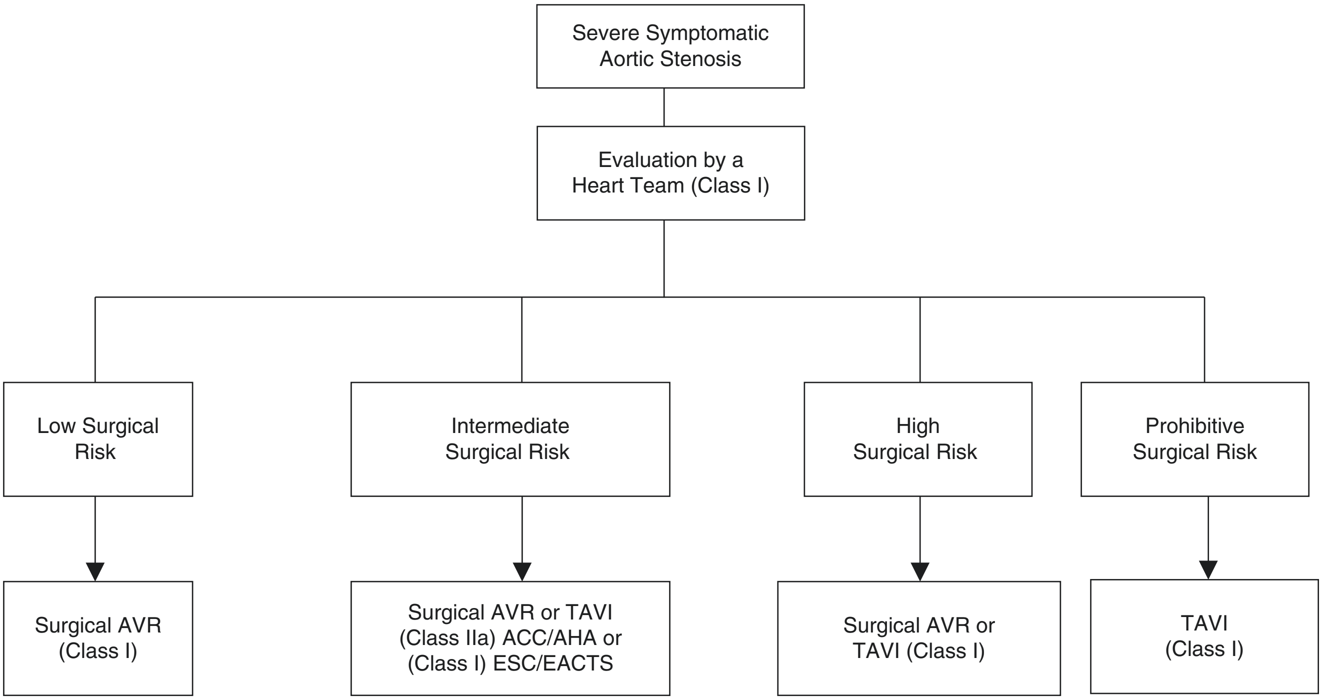
Severe Symptomatic Aortic Stenosis
Evaluation by a Heart Team (Class I)
Low Surgical Risk
Intermediate Surgical Risk
High Surgical Risk
Prohibitive Surgical Risk
Surgical AVR (Class I)
Surgical AVR or TAVI (Class IIa) ACC/AHA or (Class I) ESC/EACTS
Surgical AVR or TAVI (Class I)
TAVI (Class I)

Fig. 48.3 TAVI indications

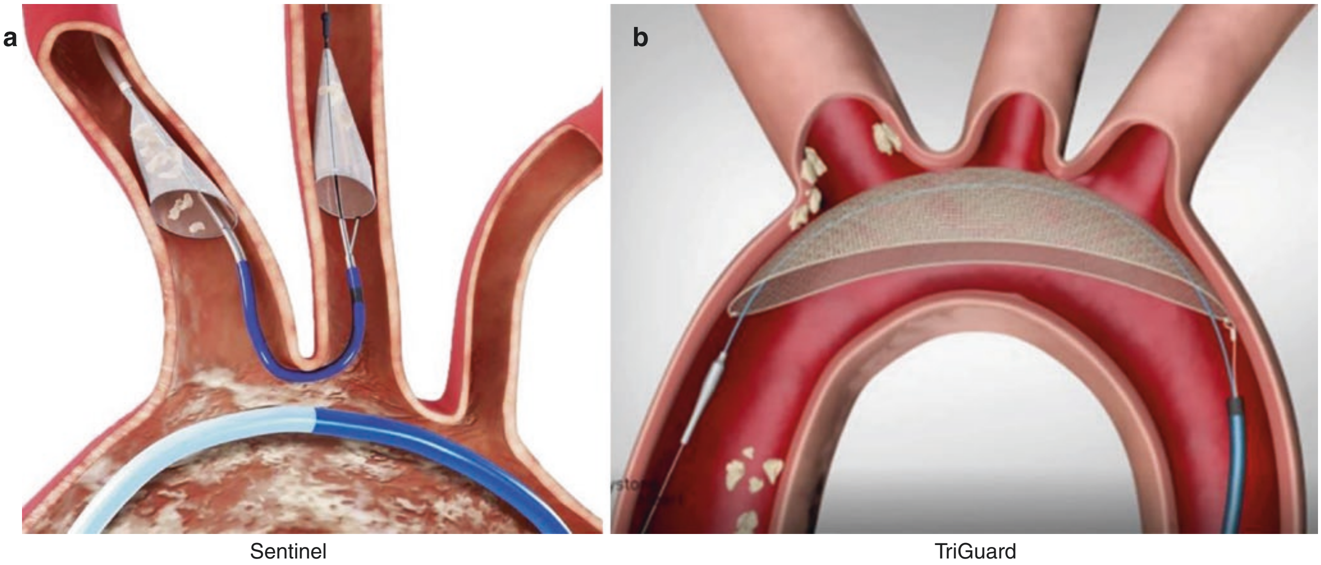

Fig. 48.4 Cerebrovascular protection devices. (**a**) *Adapted with permission from Boston Scientific.* (**b**) *Adapted with permission from Keystone Heart*

Cerebrovascular embolic protection devices have been utilized infrequently during TAVI procedures. MISTRAL-C [30] was the first randomized controlled trial that included 65 TAVI patients to receive the dual filter Sentinel (Claret Medical Inc. Santa Rosa, CA, USA) device (Fig. 48.4a) which showed a significant reduction in new lesion volume detected by diffusion weighted magnetic resonance imaging (MRI). Subsequently CLEAN-TAVI trial [31] studied the dual filter system in 100 randomized patients where it showed a reduction in new brain lesions but with similar stroke rates between device and control groups. SENTINEL trial [32] randomized 363 patients to control arm, imaging device arm and safety arm in a 1:1:1 ratio. There was no significant difference in major adverse cardiac and cerebrovascular event rates or new lesion volume on MRI at 30 days. Another cerebrovascular protection device was later introduced. TriGuard (Keystone Heart) (Fig. 48.4b) that provides protection to the three major aortic arch branches compared to Sentinel where the left subclavian artery remains unprotected. It was studied in the DEFLECT trial [33] where it randomized 46 patients to TriGuard device and 39 control patients. There was 57% higher incidence of freedom of ischemic lesions in the device arm. In conclusion, cerebral protection devices showed potential for clinical benefit however, the lack of definitive data to support them has led to infrequent utilization.

Valve Thrombosis and Antithrombotic Management

Leaflet thrombosis following TAVI is a relatively frequent finding in patients with increase in prosthetic gradients. Recently, the Low Risk Trial found that 14% of patients had evidence of subclinical leaflet thrombosis at 30 days. Several studies found that the absence of post-procedural oral anticoagulation as well as larger THV were predictive of leaflet thrombosis [34]. Optimal antiplatelet or anticoagulation regimen after TAVI is still unclear. The current guidelines recommend dual antiplatelet management with aspirin and clopidogrel for up to 6 months after the procedure [35]. However, the results of three randomized trials (Table 48.3) [36–38] as well as expert consensus have prompted great variation in the anti-platelet regimens post TAVI in the clinical practice. Although, there is no evidence of any benefit

Table 48.3 Summary of the randomized trials evaluating antithrombotic management after TAVI

Randomized trial	Methodology		
	DAPT	SAPT	Outcomes
Ussia et al. 2012 [36]	Lifelong aspirin + 3 months clopidogrel	Lifelong aspirin alone	• No significant reduction in MACCE at 30-days or 6-months
Stabile et al. 2014 [37]	Lifelong aspirin + 6 months clopidogrel or ticlopidine	Lifelong aspirin alone	• No significant difference in mortality or neurological events • Significant increase in vascular complications with DAPT
Rodes-Cabau et al. 2017 [38] ARTE Trial	Aspirin for at least 6 months + clopidogrel for 3 months	Aspirin for at least 6 months	• SAPT reduced the risk of major bleeding without increasing the risk of MI or stroke

DAPT dual antiplatelet therapy, *SAPT* single antiplatelet therapy, *MACCE* major adverse cardiac and cerebrovascular events, *MI* myocardial infarction beyond aspirin alone, larger trials are still needed to establish the optimal therapy.

Conclusion

TAVI has emerged as the standard therapy for patients at prohibitive, high and intermediate risk for surgery. With the imminent expansion into lower risk patients, long-term durability, stroke, PPM and paravalvular leaks remain challenging issues. The Heart Team is pivotal to determine the optimal treatment for each patient based on the risk evaluations, frailty, comorbidities and patient preference.

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Transcatheter Pulmonary Valve Replacement

Hussam S. Suradi and Ziyad M. Hijazi

High Yield Facts

- Transcatheter pulmonary valve replacement has evolved over the past decade as an attractive alternative to surgery in patients with right ventricular outflow tract dysfunction.
- Transcatheter pulmonary valve replacement is intended to extend the lifetime of a right ventricle-to-pulmonary artery conduit and hence reduces the number of open-heart surgeries required over a patient's lifetime.
- Multiple clinical trials have demonstrated effective restoration of valvular competence with excellent outcomes.
- Procedural success is generally high, with mean valve deployment of 95%.
- The mean procedural major complication rate is just greater than 4%.
- The overall mean freedom from reintervention is 86% over a mean follow-up of 26 months.
- Application of this technology has been extended further to patients with native right ventricular outflow tract dysfunction and those with failing pulmonary bioprosthetic valves.

Introduction

Transcatheter pulmonary valve replacement (tPVR) is one of the most exciting recent developments in the treatment of structural heart disease and has evolved as an attractive alternative to surgery in patients with dysfunctional right ventricle-pulmonary artery conduits. Although surgical pulmonary valve replacement is associated with low morbidity and mortality rates, there are many instances when operative risks are high or surgery is prohibitive [1]. Patients requiring right ventricular outflow tract (RVOT) reconstruction require multiple sternotomies and cardiac surgical procedures throughout their lives due to the limited lifespan of such conduits [2]. Patient management strategies have, therefore, been based on delaying surgical intervention for as long as possible, in order to minimize the number of surgical procedures. However, this approach carries the risk of delaying surgery beyond a point of irreversible right ventricular (RV) dysfunction. A balance between the deleterious effects of RVOT dysfunction and the need to minimize the total number of lifetime surgeries for a given patient is a clinically challenging task prompting the need to develop minimally invasive valve therapies.

Since the introduction of tPVR in 2000 [3], the learning curve with this technology has led to significant improvements in both valve design and procedural approach, with several clinical trials demonstrating the safety and efficacy in restoring valvular competence with excellent short to medium term outcomes [4–6]; transforming this technique from its early pioneering nature into routine clinical care at specialized centers. Evolving data from these studies have shown beneficial effects of tPVR in RV volume reduction [7], left ventricular (LV) filling properties [8], exercise capacity [9] and electrical remodeling [10].

Indications and Patient Selection

To establish clinical indications criteria, all patients undergo a standardized assessment protocol to ensure appropriate patient

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selection. Echocardiography is usually the initial screening tool to determine the RVOT gradient, RV pressure, RV to LV pressure ratio and to semi quantitatively assess the severity of pulmonary regurgitation. Recent advances in cardiac magnetic resonance imaging (MRI) allow detailed quantitative assessment of the structure of the RV as well as the flow dynamics in the setting of pulmonary homograft dysfunction [11]. This quantitative assessment aids in the clinical determination of the need and timing of re-intervention in asymptomatic patients.

Present indications for tPVR have been adapted from those accepted for surgical PVR (Table 49.1). The scientific statement from AHA on indications for intervention in pediatric cardiac diseases advocates tPVR in a patient with an RV-to-pulmonary artery conduit with associated moderate-to-severe pulmonary regurgitation or stenosis provided the patient meets inclusion/exclusion criteria for the available valve (Class IIa) (Table 49.2) [12].

Two other important indications for intervention include the risk for longer-term arrhythmia and progressive LV dysfunction. QRS duration ≥180 ms have been associated with 42-fold increased risk of sustained ventricular tachycardia and a 2.2-fold increased risk of sudden cardiac death during a 10 year follow up study [14]. tPVR has been found to significantly reduce QRS duration in those with predominant regurgitation and therefore may affect arrhythmia burden in this patient group [10]. LV dysfunction has been seen in approximately 20% of adult patients with repaired tetralogy of Fallot [15]. The exact mechanisms underlying LV dysfunction are not clear, but ventricular diastolic interaction, along with prolonged abnormal electrical remodeling may be involved. The impact of tPVR on LV dynamics has shown small but significant increases in LV ejection fraction [13, 16].

Table 49.1 Indications for pulmonary valve replacement

• Presence of symptoms
• Indexed RVEDV >150 ml/m^2 ± regurgitant fraction >40%
• RVOT peak instantaneous gradient >50 mmHg
• RV dysfunction (RVEF <40%)
• Moderate-severe accompanying tricuspid regurgitation

RV right ventricular, *RVEF* right ventricular ejection fraction, *RVEDV* right ventricular end-diastolic volume, *RVOT* right ventricular outflow tract

Table 49.2 Inclusion criteria for clinical trials with both the Melody® and SAPIEN™ valves

Melody® (Ref. 12)	SAPIEN™ (Ref. 13)
Age ≥ 5 years/weight ≥ 30 kg	Weight > 35 kg
Original conduit diameter ≥ 16 mm	In situ conduit ≥16 mm and ≤24 mm
Echocardiographic RVOT conduit dysfunction	≥ +3 PR (TTE) or PRF > 40% (MRI)
• Patients classified as NYHA class II, III, or IV: Doppler mean gradient ≥35 mmHg or ≥ moderate PR	With or without stenosis
• Patients classified as NYHA class I: Doppler mean gradient ≥40 mmHg or severe PR associated with TV annulus z-score ≥2 or RVEF <40%	

PR pulmonary regurgitation, *PRF* pulmonary regurgitation fraction, *RVEF* right ventricular ejection fraction, *TTE* transthoracic echocardiography, *TV* tricuspid valve

In addition to clinical indications, several anatomical criteria need to be fulfilled to qualify for tPVR. The ideal anatomy for tPVR is a uniform diameter from RVOT to pulmonary artery with adequate main pulmonary artery length to avoid stenting into the pulmonary artery bifurcation. With the current iterations of the Melody valve, the RVOT, pulmonary valve annulus, and proximal main pulmonary artery must be 22 mm or less to prevent leaflet malcoaptation. Using the 22 mm Ensemble delivery system, the outer diameter of the Melody valve is approximately 24 mm, and therefore any inner diameter of a conduit larger than this would be insufficient to securely anchor the valve. Nevertheless, there is limited experience with mounting the Melody valve on a 24 mm balloon delivered through a 24 French sheath [17]. The SAPIEN valve can be deployed in RVOT sizes up to 29 mm in diameter.

Furthermore, assessing the course of the proximal coronary arteries in relation to the RVOT is crucial prior to tPVR. The coronary arteries can run in close proximity to the RVOT carrying the risk of coronary artery obstruction due to expansion of the RVOT [18]. This proximity that may preclude a tPVR is present in about 5% of patients [19].

Current Technologies

Medtronic Melody Transcatheter Pulmonary Valve

The Melody valve (Medtronic Inc., Minneapolis, MN) consists of a harvested valve from a bovine jugular vein that is sutured into a platinum-iridium stent frame that is 28 mm long, and is mounted on different balloon diameters, ranging from 16 mm to 22 mm in 2 mm increments (Fig. 49.1). The stent is crimped onto the Ensemble delivery balloon system and can be expanded up to 22 mm diameter. The system is a 22 French catheter comprising a balloon-in-balloon deployment design. The tip of the system is blue to correspond with the outflow suture of the stent. There is a retractable sheath that covers the stented valve during delivery and is pulled back just prior to deployment. Contrast can be injected via the retracted sheath from a side port to confirm positioning prior to valve deployment. Proximally there are three ports: one for the guidewire (Green), one for inner balloon inflation (Indigo) and one for outer balloon inflation (Orange).

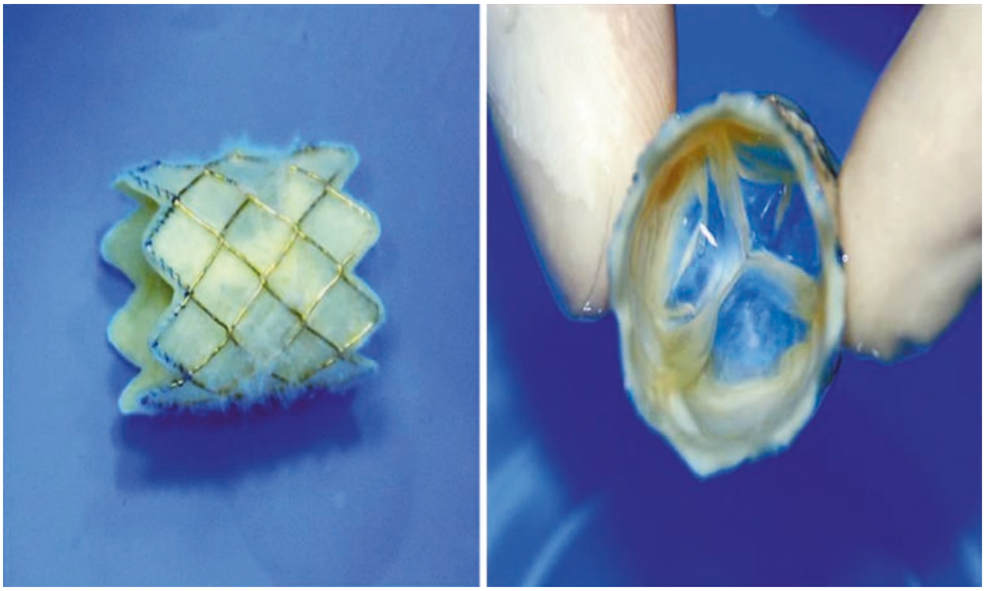

Fig. 49.1 The Medtronic Melody pulmonary valve; long axis (left) and short axis views (right)

Edwards SAPIEN Transcatheter Heart Valve

The old SAPIEN valve is a trileaflet bioprosthesis made of bovine pericardium that is mounted on a balloon-expandable stainless steel stent (Fig. 49.2a). The stent has a fabric cuff placed in the ventricular side that covers one half of the frame, limiting stent expansion and decreasing paravalvular insufficiency. The valve is available in 23 and 26 mm sizes allowing for implantation in larger RVOTs than the Melody valve. The second-generation device, SAPIEN XT valve is made of cobalt-chromium alloy that provides the same radial strength yet reduces the valve profile. This valve is available in 20, 23, 26, and 29 mm sizes (Fig. 49.2b). The newest balloon-expandable valve addition is the SAPIEN 3 THV (Fig. 49.2c). As with earlier devices, the inflow of the SAPIEN 3 is covered by an inner polyethylene terephthalate; however, it has an additional outer polyethylene terephthalate to enhance paravalvular sealing effect. SAPIEN 3 is available in four sizes, 20, 23, 26 and 29 mm diameter. Each size of valve is supplied with a matched delivery system, which incorporates an appropriately sized noncompliant high-pressure balloon. The valve is tightly crimped onto the balloon shaft utilizing a specialized manual crimping tool.

Table 49.3 outlines the main differences between the SAPIEN and Melody valve.

The Procedure and Technical Considerations

Transcatheter pulmonary valve replacement is usually performed under general anesthesia with biplane fluoroscopic guidance. Femoral approach is usually chosen due to the setup of the catheterization lab; alternatively, jugular access can be preferentially selected to provide a more favorable anatomic curvature for device delivery. Pretreatment with intravenous antibiotics and loading with aspirin before valve implantation are recommended. Intra-procedural heparin is required to maintain activated clotting time (ACT) longer than 200 s. Right heart catheterization is initially performed to assess pressures and saturations with special attention to any relevant pulmonary branch stenosis. The balloon-tipped catheter is then replaced with a stiff guidewire (0.035″ Amplatzer extra stiff (AGA Medical, Plymouth, MN) or Lunderquist ultra stiff (Cook, Bloomington, IN)) and positioned into a distal branch pulmonary artery, preferably the left lower branch given its vertical orientation, to provide adequate support to advance the delivery system. Great care is needed for maintaining wire stability during device advancement to avoid the risk of pulmonary artery injury. Biplane main pulmonary artery angiography is performed to assess the proposed site for device implantation and quantification of pulmonary regurgitation. Implantation site dimension is then measured using a compliant sizing balloon (St Jude Medical, Plymouth, MN). Simultaneous coronary angiography should be performed during full balloon inflation to assess the course and proximity of the coronary arteries to the RVOT due to the risk of compression with RVOT expansion [18]. Typically, lateral and LAO/caudal projections profile the left coronary artery very well in relation to the balloon position. Potential coronary artery compression is not uncommon with 4.4% of the US cohort demonstrating unsuitable anatomy [4], and deaths have been reported as a consequence of coronary compression in this setting. Either coronary artery may be at risk, although the left main or proximal left anterior descending arteries are the most often affected. Although non-invasive testing may demonstrate

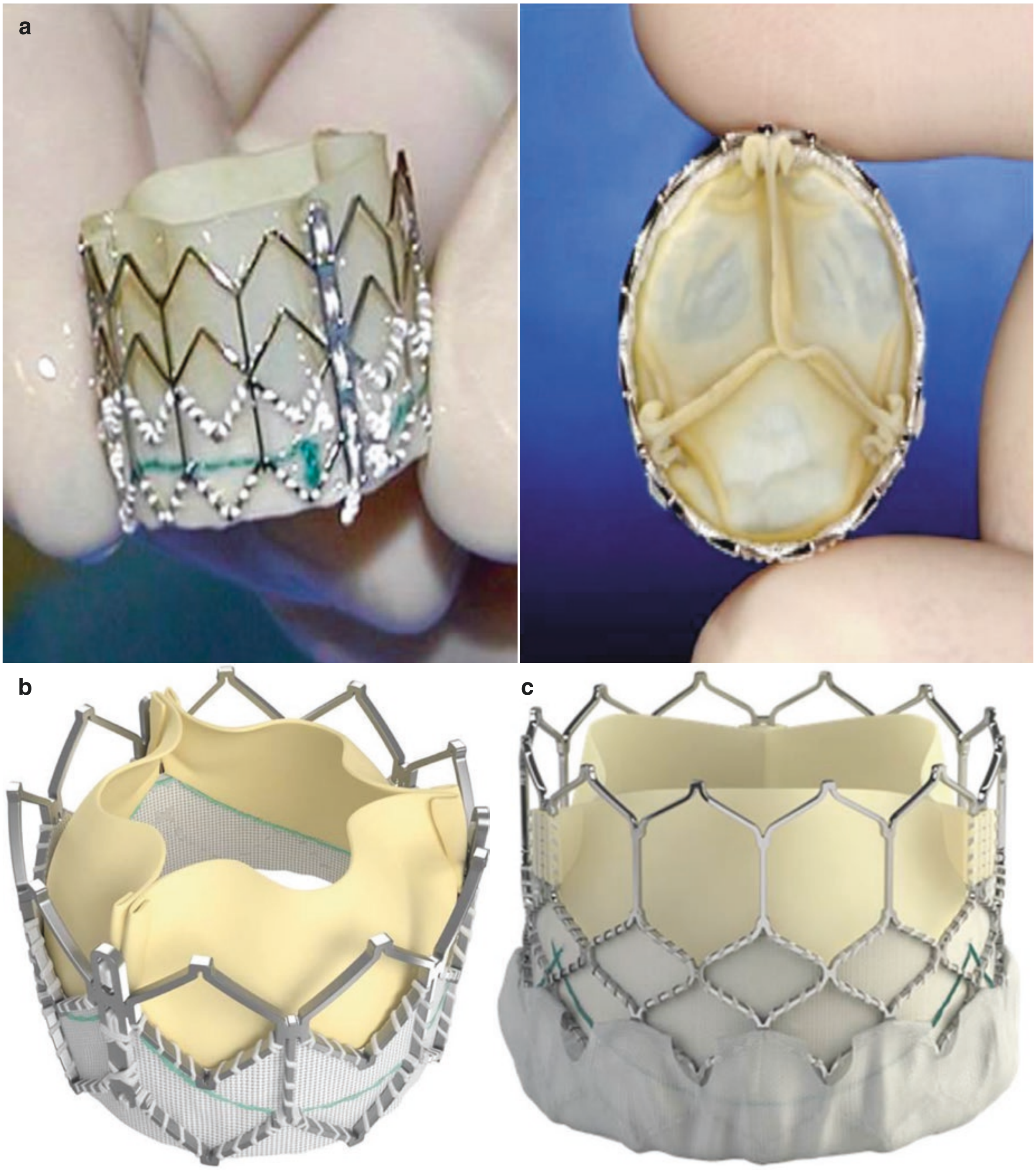

Fig. 49.2 (**a**) Edwards SAPIEN valve; long axis (left) and short axis views (right). (**b**) SAPIEN XT valve. (**c**) SAPIEN 3

Table 49.3 Comparison of Melody® and the SAPIEN™ valves

Characteristics	Melody® valve	SAPIEN™ valve	SAPIEN XT	Sapien 3
Stent material	Iridium 10% Platinum 90%	Stainless steel	Cobalt chromium	Cobalt chromium
Valve material	Bovine jugular vein	Bovine pericardium	Bovine pericardium	Bovine pericardium
Available diameter (mm)	18–22	23, 26	20, 23, 26, 29	20, 23, 26, 29
Delivery sheath size (Fr)	22	22 or 24	16, 18 or 20	14 or 16
Prestenting	Recommended	Required	Required	Required
Stent fracture	21%	None reported	None reported	None reported

significant distance between RVOT and coronary arteries, all patients should have simultaneous coronary angiogram with balloon inflation of the outflow tract. If coronary compression is documented, the procedure has to be aborted [20]. In cases of significant conduit obstruction, gradual balloon dilation of the conduit is performed until a suitable and final size is achieved to assess for coronary compression. This is then followed by the stenting step (see below).

Pre-stenting of the conduit with a bare metal stent has several advantages. It is required in almost all cases (for Edwards valve) to provide a landing zone for the stented valve, to reduce the risk of stent fracture (for Melody valve), to maintain a circular configuration of the valve in the long term, and in case of the SAPIEN valve to allow greater margin of safety when positioning the relatively short valve prosthesis (14–19 mm) which would not cover the whole length of conduit or pulmonary trunk obstruction. The stent is typically deployed on a BiB (balloon-in-balloon) catheter (NuMED Inc., Hopkinton, New York) to a diameter of up to 2 mm less than the original conduit size in stenotic conduits or slightly larger in conduits without stenosis. In the United States, we typically use the balloon-expandable IntraStent (ev3, Plymouth, MN) or the Palmaz XL stents; outside the United States, there are more choices of stents. In addition to the above, one potentially can use: the CP stent (NuMED) or the AndraStent (AndraMed Medical Devices, Germany). Covered stents, when available, can be alternatively used if there are concerns of conduit rupture due to calcification. Post-dilatation of the stent using a non-compliant balloon may be needed to achieve the intended diameter. Pressure measurements after stenting should document no to minimal (<15 mmHg) residual gradient across the outflow tract prior to proceeding with device implantation. It is crucial to recognize the potential deleterious effects of residual stenosis on exercise capacity and valve degeneration with higher RVOT gradients after tPVR; thus, attempts should be made to abolish any residual gradient before proceeding with valve implantation [5]. The appropriate device size is then selected based on the diameter of the balloon at full inflation during pre-stenting. For the Melody valve, the choice of Ensemble delivery system depends upon the size of the conduit (16, 18, 20 or 22 mm). As for the SAPIEN valve, prosthesis size is determined based on the diameter of stented conduit. For the 23 mm valve, a final stent conduit should be no less than 21 mm and for the 26 mm, a final conduit diameter should not be less than 24 mm.

After appropriate device selection and preparation, the delivery system is advanced over the guidewire, bringing the valve into the implantation site. A maneuver that can facilitate advancing the delivery system when it is at the entrance of the conduit is looping the system within the right atrium. This generates a forward force aiding passage into the conduit. Once the Melody valve is in the appropriate position, it is unsheathed followed by gradual inflation of the inner then the outer balloons. Slow inflation allows time to adjust the position in the event of device slippage. Similarly, the SAPIEN valve is inflated on a single balloon slowly. Repeat angiography and pressure measurements are made to confirm a positive outcome. Occasionally, the implanted valve may require post dilatation with a non-compliant balloon. Fluoroscopic steps and echocardiographic results of SAPIEN valve deployment are depicted in Figs. 49.3 and 49.4, respectively.

Once the procedure is complete, we routinely perform figure-of-eight suture to achieve hemostasis. Some operators prefer preclosing the femoral venous access site with the suture-mediated Proglide device (Abbott Inc., Redwood City, CA). Patients are typically observed overnight in telemetry wards. Empiric IV antibiotics are administered. The following day, ECG, PA/lateral chest X-ray and transthoracic

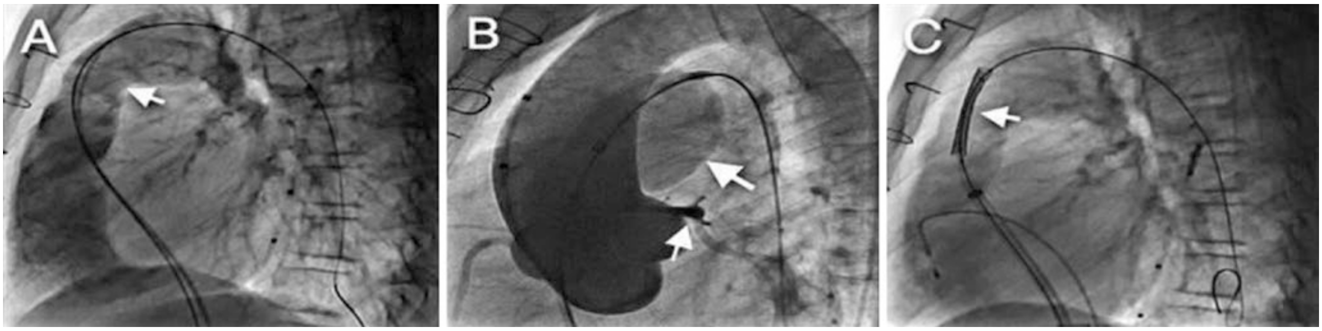

Fig. 49.3 SAPIEN valve placement steps. (**a**) Pulmonary homograft angiography demonstrates severe pulmonic regurgitation. (**b**) Conduit balloon sizing with simultaneous aortic root angiography (large arrow shows the balloon inflation in the conduit, small arrow demonstrates left coronary artery with an acceptable distance from the conduit). (**c**) Bare metal stent placement in conduit with hand injection angiography to delineate stent position. (**d**) Balloon stent deployment. (**e**) Angiography post stent deployment demonstrating no conduit stenosis with free pulmonary regurgitation. (**f**) SAPIEN valve positioned in the middle of the stent. (**g**) Balloon deployment of the valve. (**h**) Excellent valve position inside the stent. (**i**) Final angiography in conduit demonstrating no significant pulmonary regurgitation

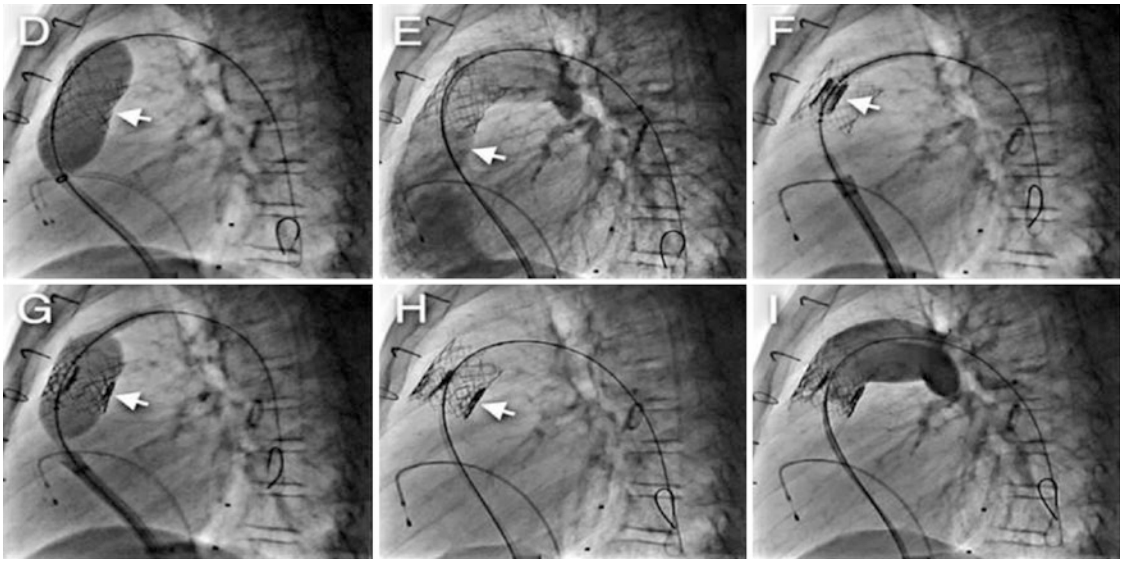

Fig. 49.3 (continued)

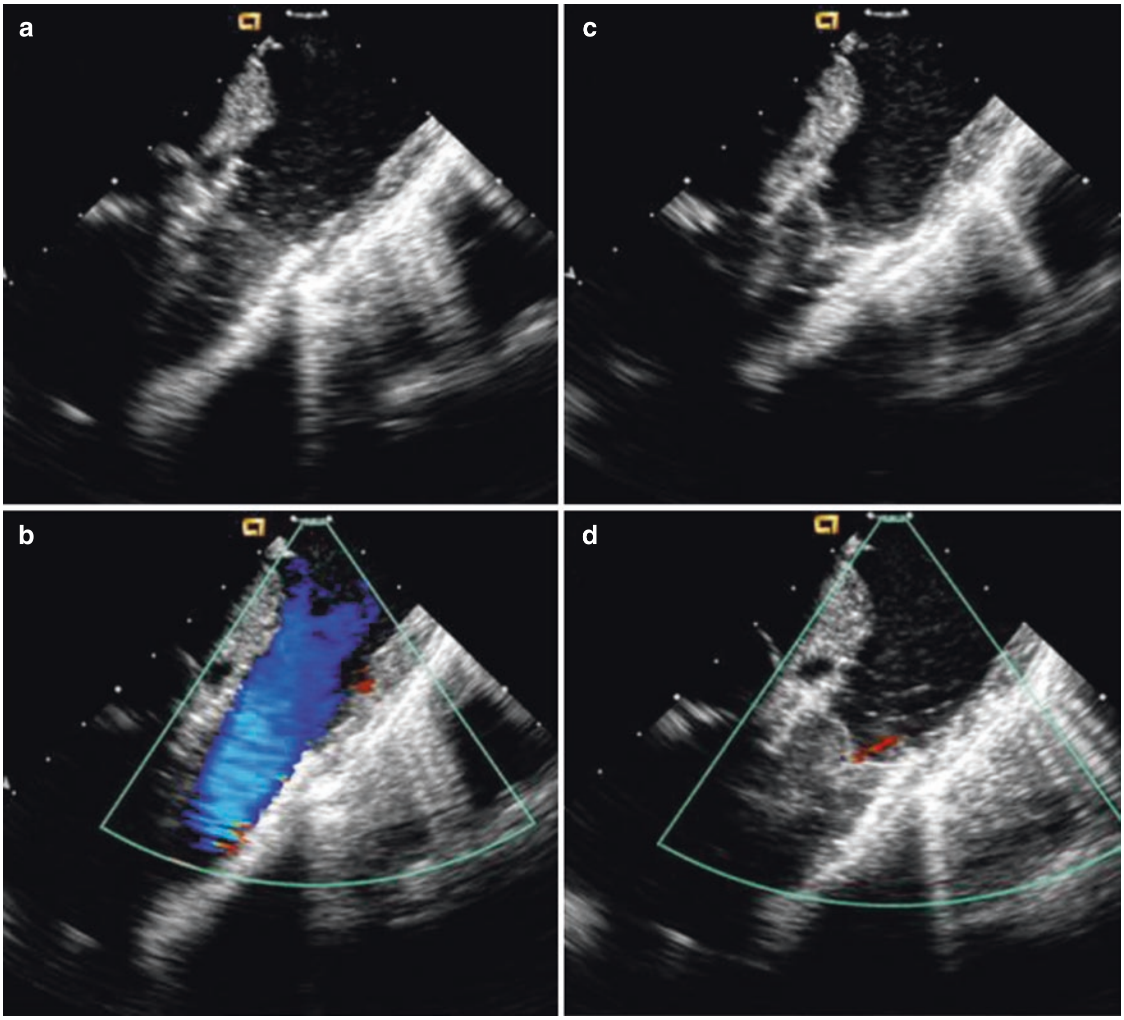

Fig. 49.4 Intracardiac echocardiography (ICE) images. (**a**) Two-dimensional ICE in systole demonstrating complete opening of SAPIEN valve leaflets. (**b**) Color Doppler in systole demonstrating no narrowing passing SAPIEN valve. (**c**) Two-dimensional ICE in diastole demonstrates complete valve closure. (**d**) Color Doppler in diastole demonstrates trivial pulmonary regurgitation

Table 49.4 Procedural outcomes from clinical studies

Investigators	N	Success rate	Procedural complications	Stent fracture	Freedom from reintervention (Follow-up)
Lurz et al. [5]	163	155 (95%)	7 (4.5%)	21%	70% (70 months)
McElhinney et al. [4]	136	124 (91%)	8 (6%)	22%	93.5% (12 months)
Eicken et al. [21]	102	100%	2 (2%)	5%	89% (12 months)
Kenny et al. [13]	36	33 (92%)	7 (20.5%)	0	97% (6 months)
Butera et al. [22]	63	61 (97%)	9(14%)	16%	81.4% (30 months)

echocardiogram should be performed. Patients are instructed to take endocarditis prophylaxis before dental procedures. As for antiplatelet therapy, there is little data supporting specific antiplatelet regimen, and to date no definite reports of thromboembolism have been reported. In our institution, we prescribe life-long low-dose aspirin. Patients are typically discharged the following day with arrangement for routine cardiology follow-up care including regular fluoroscopic evaluation.

Hemodynamic and Clinical Outcomes

Data from the largest most recently published studies evaluating attempted tPVR (Melody and SAPIEN) in 500 patients are outlined in Table 49.4. Procedural success is generally high, with mean valve deployment of 95%. The mean procedural major complication rate is just greater than 4%. The overall mean freedom from reintervention is 86% over a mean follow-up of 26 months. The most common reason for reintervention with the Melody valve is stent fracture despite pre-stenting (5–16%). Stent fracture has not been reported to date with the SAPIEN valve. The risk of infective endocarditis has been reported consistently between 1% and 4% with the Melody valve [23].

The longest and largest published experience to date, the US Melody valve Investigational Device Exemption trial, reported 150 valve implants, with all patients at least 4 years from implant, and longest follow-up to 7 years [24]. tPVR resulted in acute reduction of RV pressure to a median of 42 mmHg and a reduction in peak gradient across the RVOT to a median of 12 mmHg. All patients had no or trace pulmonary regurgitation except one with moderate pulmonary regurgitation. Overall periprocedural mortality or other serious complications were low. Freedom from Melody valve dysfunction was 94% at 1 year, 86% at 2 years and 76% at 5 years. Stent fracture was documented in 50 patients, with the majority being managed with further catheter intervention.

The COMPASSION trial (**CO**ngenital **M**ulticenter trial of **P**ulmonic v**A**lve regurgitation **S**tudying the **S**APIEN **i**ntervent**ION**al) was the first prospective multicenter study to assess the safety and efficacy of the SAPIEN THV for the treatment of dysfunctional RV-PA conduits with moderate to severe pulmonary regurgitation with or without stenosis [13]. Among 36 patients, successful valve deployment was achieved in 33 of 34 attempts. Pullback peak-to-peak systolic gradient across the conduit decreased from 27 to 12 mmHg ($p < 0.001$). At 6 months follow-up, the number of patients in NYHA functional class I increased from 5 at baseline to 27. Pulmonic regurgitation was moderate or less in 97% of patients.

Table 49.5 Procedural complications after percutaneous pulmonary valve replacement

- Death
- Stent fracture
- Coronary impingement
- Device embolization
- Paravalvular leak
- Hammock effect
- Homograft rupture
- Venous thrombosis
- Infective endocarditis
- Thromboembolism
- Valve stenosis or regurgitation

Complications

Possible device and procedural complications after tPVR are outlined in Table 49.5. Acute hemodynamic deterioration during the procedure can result from (1) obstruction of pulmonary blood flow caused by valve dislodgement into the pulmonary arteries, (2) coronary ischemia resulting from coronary impingement and (3) hemorrhage resulting from conduit rupture. The rate of serious complications in the US Melody trial was reported at 6%, including death from coronary dissection (n = 1), conduit rupture (n = 1), unstable arrhythmia (n = 1), wire perforation in distal pulmonary artery (n = 2), and femoral vein thrombosis (n = 1). In the COMPASSION trial, the rate of serious complications was 21% (7 patients). Valve or stent migration occurred in four patients (three requiring surgical retrieval and one was deployed in the inferior vena cava), unstable arrhythmias in one patient, and self-limited wire perforation in the distal pulmonary arteries in two patients.

The Future

The aim of tPVR is to prolong the life span of conduits which were surgically placed from the right ventricle to the pulmonary artery. This prolonged conduit life span should reduce the number of multiple open-heart operations over the total life span of children and young adults with congenital heart disease and potentially improve life expectancy of these patients.

Although tPVR has been described in patients with native outflow tracts [7, 16], size restriction on the currently available valves prevents deployment in the majority of patients in this setting. One of the major challenges for the future is to expand tPVR to a broader population of patients, especially those with native outflow tracts, as size and design restriction on the currently available valves prevents deployment in the majority of patients (>70%) in this setting. With significantly dilated RVOTs, hybrid surgical approaches have been described using off-pump RVOT ring placement along with tPVR. New self-expanding valve systems are in development and currently undergoing clinical trials in patients with native RVOT (Venus P valve, Venus Medtech and Harmony valve, Medtronic). The initial results from the use of these valves are encouraging [18, 25]. In addition to these two new valves, a new stent (Right ventricle outflow tract reducer) called Altera from Edwards is being evaluated in the United States with potential implantation of the Edwards Sapien 3 valve inside, thus allowing the use of currently available and approved valve to help patients with large right ventricle outflow tract.

Ultimately, future aspirations must include efforts to merge these approaches with tissue engineering technologies to provide living autologous valve replacements with growth potential. The concept of a "living valve" delivered on a bioresorbable scaffold with the potential to grow with the patient is one of the final destinations of this exciting journey.

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Transcatheter Mitral Valve Therapies

50

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High Yield Facts

- Transcatheter mitral valve (MV) treatment (repair/replacement) has evolved over the past few years as an attractive alternative to surgery in patients with symptomatic MV regurgitation and high surgical risk.
- Percutaneous MV repair devices are generally based on the same principles as MV surgery: neochordae placement, leaflet plication, annuloplasty, papillary muscle modification, and left ventricular (LV) remodeling.
- Catheter-based devices and techniques can be grouped into those acting on the leaflets and subvalvular apparatus, annuloplasty (direct/indirect), and chamber (LV) remodeling.
- There are two “percutaneous mechanical sutures” for edge-to-edge repair: PASCAL and MitraClip.
- MitraClip® is the most widely used (>60,000 implants) and the only one alluded to in the international guidelines.
- Most recently, a large number of transcatheter valves have also emerged for percutaneous placement in the mitral position.

Introduction

Mitral regurgitation (MR) is one of the most prevalent valvular heart diseases in Western countries. Its prevalence increases with age resulting in over 10% of the population aged 75 years and older affected by it [1]. It is the second most common valvular heart lesion requiring surgery after aortic valve replacement [2]. The mitral valve (MV) is a complex apparatus. Any structural change in this apparatus (i.e., leaflet prolapse, chordal rupture, or myxomatous MV disease) can lead to primary (degenerative) MV regurgitation (DMR). Likewise, anatomical changes (i.e., dilation) of the left atrium, MV annulus, or left ventricle (LV) can lead to secondary (functional) MV regurgitation (FMR) [3]. Conventional open surgery provides excellent results in young patients without comorbidities, but, up to 50% of patients hospitalized with severe MR are not referred for surgery because of high surgical risk [4]. Transcatheter valve interventions have recently emerged as an option to treat inoperable or high-risk patients who are not suitable for conventional open-heart surgery [5].

Percutaneous MV repair devices are generally based on the same principles as MV surgery: neochordae placement, leaflet plication, annuloplasty, papillary muscle modification, and LV remodeling.

Current Transcatheter Management of Mitral Regurgitation

Catheter-based devices and techniques have appeared and multiplied so rapidly that it is almost impossible to describe all of them. They can be grouped into those acting on the leaflets and sub-valvular apparatus, direct (DA) or indirect annuloplasty (IA), and chamber (LV) remodeling. Some have already been abandoned. For majority of the percutaneous technologies used for MV repair, the surgical background of annuloplasty and leaflet repair has been adapted.

Percutaneous Leaflet Repair

Based on the surgical Alfieri edge-to-edge repair [6], there are two “percutaneous mechanical sutures”: the MitraClip® (Abbott Laboratories, Abbott Park, IL) device and the novel Edwards PASCAL transcatheter MV repair (TMVr) system

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(Edwards Lifesciences, Irvine, CA, USA). The MitraClip® is the only one incorporated into the international guidelines.

The MitraClip® has been used in more than 60,000 implants and received CE mark approval in 2008 and FDA approval in 2013 for patients with severe DMR who are at prohibitive or high surgical risk [7]. This is a polyester-covered cobalt-chromium mechanical clip with extending arms, which works as "mechanical suture" permanently grasping both mitral leaflets. Consequently, the sub-valvular apparatus is spared, and a double orifice is created improving leaflet coaptation minimizing MR.

To implant the device, a 24-French (Fr) delivery catheter is introduced via the femoral vein (FV) into the right atrium (RA) and, after transseptal puncture (TSP), advanced into the left atrium (LA). Under 2-dimensional and 3-dimensional transesophageal echocardiographic (TEE) and fluoroscopic guidance, the clip is positioned above the MV. Once opened, it is advanced into the LV and subsequently, retracted, and the free edges of the mitral leaflets are loaded onto the clip. Then, grippers and arms are closed to grasp them permanently.

The system was initially evaluated in the EVEREST-I and EVEREST-II randomized trials. After the first-in-human experience in 2003, EVEREST-I in 2005, a 6-month follow-up of 27 patients, reported no procedural complications. Six patients underwent elective valve surgery (three because of partial clip detachment and three for unresolved MR). After 6 months, 13 of 14 patients had MR reduction to ≤2+ [8]. The EVEREST-II trial then randomized 279 patients in a 2:1 ratio to undergo either percutaneous repair (n = 184) or MV surgery (n = 95). At 5-years follow-up, recruiting 73% of patients with DMR, it demonstrated relatively low rates of surgery for MV dysfunction, endorsing the durability of MR reduction with the technique [9].

Apart from randomized trials, there are also registries and single-arm studies in a real-world setting reporting outcomes for a large number of patients with FMR. ACCESS-EU [5], TRAMI [10] and European Sentinel are the largest registries in terms of number of patients (Table 50.1). All these registries indicate that the edge-to-edge percutaneous technique with MitraClip® is secure (3% mortality), feasible (94% procedure success) and effective (80% with MR ≤+2 and New York Heart Association [NYHA] class = II after 1 year).

There are three ongoing randomized trials (COAPT [11], RESHAPE-HF [12] and MITRA-FR [13]), comparing the efficacy of MitraClip® with optimal medical treatment in inoperable patients with FMR.

The novel Edwards PASCAL device has been designed to address some limitations of the first generation MitraClip® system. It has some theoretical advantages over MitraClip®, with simpler navigation in the LA (the system entails less dependency on trans-septal puncture (TSP) height), using a central spacer to improve MR reduction (to minimize the intra-prosthesis regurgitation), as well as enabling independent leaflet grasping.

The first report with this device involved 23 compassionate patients with grade >3 MR. With a 9% rate of periprocedural complications, after device implantation, a reduction of MR to <2+ was achieved in 96% of cases. Technical success was achieved in 96% of patients, and three patients died during 30-days follow-up [14]. Today, the CLASP trial is enrolling patients to evaluate the safety and clinical outcomes of the PASCAL system [15].

Other leaflet repair devices are under clinical development (Table 50.2).

The thermocool irrigation ablation electrode (Biosense Webster, Inc., Diamond Bar, CA), uses radiofrequency energy to produce heat in the leaflets provoking shrinking

Table 50.1 Efficacy and safety of MitraClip therapy as reported by key studies

	Randomized	Registries								Single arm		
	EVEREST II	TRAMI	European sentinel	ACCESS EU	TVT1	Estévez-Loureiro 2015	GRASP	Mitra Swiss	French	EVEREST II HRS	REALISM	Total or average
Patients (n)	184	1064	628	567	564	173	117	100	62	78.0	272.0	3809
Procedure mortality %	1	4.5	2.9	3.4	2.3	–	0.9	5	3	7.7	1.5	3
1-year mortality %	6.1	20.3	15.3	17.3	–	–	16	19	–	23.0	9.0	16.8
Procedure success	–	97	95.4	91.2	93	98	100	85	95.2	71.8	90.0	93.8
MR ≤2 at 1-year %	82	–	58.6	79	–	90	89	58	–	78.0	83.0	79.9
NYHA class II 1-year	99	–	75	70	–	70	81	70	85	74.0	92.0	77.1

MR mitral regurgitation, *NYHA* New York Heart Association

Table 50.2 Devices for mitral leaflets and chordal repair

Device	Access	Technique	Implant	MR etiology	Commercial status	Strengths	Weaknesses
MitraClip	TV/TS 24 Fr	E-T-E repair	Clip	DMR/ FMR	CE mark 2008 FDA 2013	Most used Versatility	Only leaflets repair, lack of annulus
PASCAL	TV/TS 22 Fr	E-T-E repair	Clip	DMR/ FMR	NO	Easier to use, less limitation	Only leaflets repair, lack of annulus
Thermocool	TV/TS 7.5 Fr	Leaflets ablation	None	DMR	NO	No implants	Lack of accuracy
MitraSpacer	TV/TS & TA	"Filling" MRO	Balloon	FMR	NO	Adjustable from outside	Thrombosis TS and TA access
MitraFlex	TA	Chordal implant +/– E-T-E	Synthetic chords +/– Clip	DMR	NO	Strong surgical background In the same act a Clip can be implanted	Only leaflets repair, lack of annulus
NeoChord	TA 24 Fr	Chordal implant	Synthetic chords	DMR	CE mark 2013 FDA 2016	Strong surgical background	Only leaflets repair, lack of annulus
Harpoon	TA 14 FR	Chordal implant	Synthetic chords (preformed Knot)	DMR	NO	Strong surgical background Lower profile	Only leaflets repair, lack of annulus
Babic	TA/TS	Chordal implant	Synthetic chords and an elastic polymer tube	DMR	NO		Both TA and TS access
V-Chordal	TA	Chordal Implant	Synthetic chords	DMR	NO	Is attached to a papillary muscle	Requires atriotomy

DMR degenerative mitral regurgitation, *E-T-E* edge-to-edge repair, *FMR* functional mitral regurgitation, *Fr* French, *MRO* mitral regurgitant orifice, *TA* trans-apical, *TA/TS* trans-apical/trans-septal, *TV/TS* trans-venous/trans-septal

and motion reduction ("leaflet ablation"). It has some limitations, as it depends on collagen reaction. Scarring and fibrosis could be excessive or not enough to limit leaflet mobility, and perforation or near structure damage may occur [16].

The Percu-Pro device (Cardiosolutions, Stoughton, MA) is a balloon-shaped spacer that acts as a "buoy" fixed to the LV apex, passing through the MV after a TSP, filling the gap between the leaflets, improving "coaptation" and decreasing MV regurgitation [17, 18].

Percutaneous Chordal Approach

The basic principle of this technique (supported by surgical long-term efficacy evidence) is to implant new synthetic chords or sutures fixing the leaflets to the LV, adjusting the length to achieve a better result under transesophageal echocardiogram (TEE) control. This approach is mainly for DMR.

NeoChord DS1000 (Neochord, Inc., Minnetonka, MN) is the most commonly used device receiving CE Mark approval in 2013 and FDA approval in 2016. It is used by transapical access (TA) to enter the LV, in a beating-heart setting. Once the system is introduced, the prolapsed leaflet is grasped and the ePTFE suture is deployed and attached to fix them to the LV under TEE control. The chordal length is adjusted to obtain the least possible MR. It was first tested in the TACT trial, which demonstrated 86.7% procedural success, with only 17 patients with <2+ grade MR at 30 days and only two patients undergoing reoperation for a failed repair [19]. The largest multicenter clinical experience with the NeoChord was recently published by Colli et al. involving 213 patients with a procedural success of 96.7%. At 1-year follow-up, overall survival was 98% and 75% were ≤mild MR grade. The mortality rate at 1 year was 1.9% [20].

The MitraFlex (TransCardiac Therapeutics, Atlanta, GA) is based on the same concept and access, but fixed to the LV through an anchor [17]. The big advantage of this device is that an edge-to-edge repair can be done at the same time by deploying a clip.

The Harpoon Medical device (Harpoon Medical, Inc., Baltimore, MD) is 14 Fr with TA access for implantation of polytetrafluoroethylene artificial chords anchored to the LV epicardium to fix the prolapsed leaflet. An important feature of this system is that it automates part of the process, simplifying it with time reduction. A preformed knot is deployed on the atrial surface of the prolapsing leaflet (with assistance from a stabilizer), away from the leaflet edge to support the leaflet and to parallelize the leaflet with the non-prolapsing leaflet, improving leaflet coaptation. The last results involving 43 consecutive patients from the early feasibility trial and the CE mark trial demonstrated after 30 days a technical success rate of 95% and 30 days procedural success of 93% with no stroke, myocardial infarction or death. There were only two surgical conversions [21].

Percutaneous Mitral Annuloplasty

TMVr annuloplasty techniques as in the surgical field, try to decrease MR by reducing MV annulus circumference, with a consequent improvement in leaflet coaptation. There are several devices available for percutaneous mitral annuloplasty, and these can be divided into two types, direct and indirect. Direct annuloplasty (DA) devices try to reduce MR from the annulus whereas indirect annuloplasty (IA) devices attempt to reduce posterior mitral annulus (MA) size from neighboring structures (Table 50.3).

Direct annuloplasty: The Cardioband technique (Edwards Lifesciences; Irvine, USA) is a transcatheter-implantable "surgical-like" ring that uses the concept of surgical MV restrictive annuloplasty [22]. The device consists of three components: the trans-septal steerable sheath (TSS) is a guiding catheter, the implant deployment system (IDS) allows anchor deployment and the size adjustment tool (SAT) is the cinching mechanism. The procedure is straightforward and reproducible with each step being reversible. In a beating heart setting, under TEE, the anterolateral commissural area (atrial side) is reached by FV and a standard TSP. During implantation, from 12 to 17 metal anchors 6 mm long are inserted to fixate the Cardioband to the tissue from anterolateral through anterior annulus to the anteroseptal commissure. Afterwards, cinching of the band translates into an approximately 30% reduction of the mitral annular diameter [23]. The device received the CE mark for MR in 2015. A one-year follow-up involving 38 patients was recently presented, with a high rate of technical success and no procedural deaths. It also shows a 28% average reduction in septolateral diameter maintained up to one year, with functional improvement measured by the 6-min walk test and the NYHA class demonstrating that the procedure is effective and durable over that time [24].

Table 50.3 Devices for direct mitral annulus treatment

Device	Access	Technique	Implant	Place	MR etiology	Clinical status	Strengths	Weaknesses
Cardioband	TV/TS 25 Fr	DA	Flexible surgical-like ring fixed by anchors and adjustable by a nitinol wire	Atrial site of the anterior MA	FMR mainly	CE mark 2015	Strong surgical background Alive-heart beating adjustment	Complex system and images guide
Mitralign	TA/ TVr	DA	Pairs of pledgeted sutures over posterior MA	Ventricular site of the posterior MA	FMR	CE mark 2016	Alive-heart beating adjustment	AA, only posterior MA
Accucinch	TLV	DA	Anchors that are connected by a cable to cinch the MA	Ventricular site of the posterior MA	FMR	NO	Causes remodeling of the basal portion of the LV	AA, only posterior MA
Millipede	TLV/ TS	DA	Repositionable and retrievable complete annular ring	Ventricular site, below the posterior mitral leaflet	FMR	NO	Complete ring	
Amend	TA	DA	Complete, semirigid, D-shaped mitral ring attached by anchors	Atrial side of the mitral MA	FMR	NO	Complete ring	
Carillon	TV/TY	IA	Two self-expanding-nitinol anchors connected by a nitinol curvilinear segment	Coronary sinus	FMR	CE mark 2009	Easy to use	No immediate improvement
QuantumCor	TV/TS	IA	Uses RF to shrink collagen, resulting in remodeling of the MA	No implants. Uses a TS multiple-electrode probe to deliver the RF, then is extracted	FMR	NO	No implants	Might not be precisely controlled results
Recor	TV/TS	IA	Uses US energy to shrink collagen, resulting in MA reshaping	No implants. Uses a TS balloon to deliver the US, then is extracted	FMR	NO	No implants	Might not be precisely controlled results
Monarc	TV	IA	Uses a spring-like band anchored in the CS with self-expanding stents	Coronary sinus	FMR	NO	Easy to use	CS laceration, device fracture
Arto	TV 12 Fr	IA	Uses two anchors, deployed in the lateral and septal wall of the LA connected by a tether	LA via Coronary sinus	FMR	NO	Easy to use	

AA arterial access, *CS* coronary sinus, *DA* direct annuloplasty, *DMR* degenerative mitral regurgitation, *FMR* functional mitral regurgitation, *IA* indirect annuloplasty, *LA* left atrial, *MA* mitral annulus, *RF* radiofrequency, *TA/TVr* trans arterial and trans ventricle retrograde, *TLV* trans left ventricle, *TV/TY* trans-jugular vein, *US* ultrasound

The Mitralign (Mitralign, Tewksbury, MA, USA) uses (the surgical principles of a Kay annuloplasty) a transfemoral retrograde LV access to reach the peri-annular space to insert intra-annular pairs of pledgets connected with a suture directly on the posterior MA. Then, cinched together by a suture can reduce the size of the MA, and thus the mitral orifice area and MR. The device received the CE Mark approval in 2016. The first-in-human study involved 71 patients with an implant success of 70.4%. MR reduction occurred in only 50% of patients, but, with LV positive remodeling and symptom improvement [25].

The Accucinch (Guided Delivery Systems, Inc., Santa Clara, CA) is another DA device, using a catheter that is advanced retrogradely into the LV to position anchors in the ventricular side of the posterior annulus. All the anchors, connected by a nitinol wire to the sub-annular space, are cinched circumferentially from trigone to trigone to improve MR. The main difference with other devices is that it causes remodeling of the basal portion of the LV. Kleber, in 2013 presented data of 18 patients in whom this device achieved about 40% reduction of MR, 5 were converted to surgery and no 30-day deaths occurred [26].

Millipede (Millipede Inc., Santa Rosa, CA) is a full semirigid nitinol ring to be implanted by TSP in MA. It is implanted and driven on the atrial side and allows the ring to be adjusted because of its design with a collar zone.

The Amend device (Valcare Medical) is a semirigid, D-shaped ring implanted by TA route. Once across the mitral valve, it is fixed to posterior MA via a series of stabilizers and after that, pulling the posterior MA anteriorly, is fixed in the anterior MA. After it is fully secured to the mitral annulus, the anterior-posterior MA dimension is reduced, improving the leaflet coaptation [27]. It was first implanted in human in 2016.

Indirect annuloplasty: Some technologies for TMVr are designed to be placed in the coronary sinus (CS). The CS surrounds the postero-lateral MA, and it may allow devices, going through, to indirectly affect the MA geometry by transmitting tension from outside. Other devices are designed to reduce the MA acting through adjacent structures. IA has the potential to be simpler than DA. However, there are some obstacles using this approach, e.g. anatomical variability of the CS and the MA, or compression of the circumflex coronary artery, which lead to higher rates of complications.

The Carillon Mitral Contour System (Cardiac Dimension, Inc., Kirkland, WA, USA) uses a dedicated delivery catheter through trans-jugular access to position a distal anchor in the CS (in the great cardiac vein) to be then, passively deployed, retracting the delivery catheter, along the CS. The device consists of a curved, self-expandable nitinol arch (60, 70, and 80 mm lengths) connecting a proximal and a distal anchor. By foreshortening, the device remodels the posterior MA. It obtained CE mark approval in 2011, and the TITAN II trial, with 36 patients treated, showed improvements in clinical and echocardiographic parameters, without the wire fracture that was one of the main issues at the beginning [28]. The REDUCE FMR study is now on going and may provide answers about reducing MR regurgitant volume, safety, and the clinical efficacy of the Carillon device [29].

The Arto System (MVRx, Inc., Belmont, CA, USA), uses venous access sheaths in the right internal jugular vein and right common FV, followed by wiring the great cardiac vein, to gain TSP to the left atrium. Then, magnetically linked catheters are placed in the great cardiac vein to facilitate puncture and formation of a venous loop. The MAVERIC trial involved 11 patients and showed reduction in the effective regurgitant orifice area, regurgitant volumes and MA, which resulted in functional status improvements for 81.8% of patients in NYHA class III/IV at baseline to 54.6% in NYHA class I/II at 30-day follow-up [30].

The VenTouch system (Mardil Medical, Minneapolis, MN) was first implanted in 2014, and consists of a bladder inserted via a left thoracotomy, placed in the external part of the annulus (ventricular side), and then, filled with saline, exerting a pressure from outside that reduces the MA and MR. The system has a subcutaneous access port that can be manipulated from outside to increase or decrease the amount of saline in the bladder customizing the degree of mitral annular reduction. The system is currently being studied for human use [31].

There are other systems for IA at different stages of development (Table 50.4).

Transcatheter MV Implantation

Transcatheter MV implantation (TMVI) is emerging as an alternative treatment option for MR in patients who are not amenable to surgery or TMVr. Currently under development are the Endovalve (Micro Interventional Devices, Inc., Newtown, PA), Tendyne (Tendyne Holdings, Roseville, MI), Cardiovalve (Valtech Cardio Ltd., Or Yehuda, Israel), CardiAQ (CardiAQ valve Technologies Inc., Irvine, CA), Edwards FORTIS (Edwards Lifesciences), HighLife (HighLife Medical, Irvine, CA), MitrAssist (MitrAssist Ltd., Misgav, Israel), Neovasc Tiara (Neovasc Inc., Richmond, Canada) and Caisson (LivaNova PLC, London, UK) valves. Only Cardiovalve, Caisson and CardiAQ are available for TSP.

CardiAQ system has a transfemoral and TA version and is the first MV implanted in a human native valve. It is placed intra- and supra-annularly to preserve LV contractility and maximize the left ventricular outflow tract (LVOT) area. It consists of a bi-level, self-expanding nitinol frame. The early feasibility study is currently recruiting patients [32].

The Caisson system is a D-shaped, self-expanding nitinol frame for TSP, consisting of two main components, an

Table 50.4 Percutaneous mitral valve replacement devices

Device	Access	Valve size (mm)	Stent	Leaflets	Anchoring	Position	Recapture	LVOT obstruction	Leak	First implant date	Additional features
CardiAQ	TA/TS 33 Fr/30 Fr	30	Circular Nitinol	Bovine	MA capture with two sets of anchors	Supra-annular	No	↓↓↓	↓↓↓	Jun 2012	Intra-annular sealing tapered outflow
Caisson	TS 31 Fr	34–40	D-Shape Nitinol	Porcine	Atrial anchoring and MA feet	Supra-annular	Yes & retrievable	↓↓	↓↓	Oct 2016	SAM management
Tendyne	TA 34 Fr	28	D-shaped (out) Circular (in) Flat ring double frame design	Porcine	Apical tether is the ventricular fixation	Intra-annular	Yes & fully retrievable/ repositionable	↓↓↓	↓↓	Oct 2014	Ventricular fixation
Intrepid	TA/TS 33 Fr	27	Circular inner stent and a conformable outer fixation ring	Bovine	Outer fixation ring through a 'champagne cork' like effect	Intra-annular	Yes & repositionable	↓↓	↓↓	Sep 2014	Dual stent design
Tiara	TA 32 Fr	30, 35, 40, 45	D-Shaped	Bovine	Three ventricular anchors	Intra-annular	Yes & repositionable	↓↓↓	↓↓↓	Jan 2014	Skirt to decrease leak
Fortis	TA 42 Fr	29	Central valve body is cylindrical	Bovine	Atrial flange, tabs, clips and paddles	Intra-annular	No	↓↓	↓↓↓	Feb 2014	Skirt to decrease leak
Cardiovalve	TS 28 Fr	40–50	Cylindrical robust frame	Bovine	Anchoring and sealing elements	Intra-annular	No	↓↓↓	↓↓↓	Dec 2017	5 degrees of control
Highlife	TA/trans arterial	31	Cylindrical nitinol frame with a preformed groove	Bovine	Subannular ring	Intra-annular	No	↓	↓↓	2017	

Fr French, *TA/TS* trans-apical and trans-septal, *NA* not available, *MA* mitral annulus, *SA* supra-annular, *IA* intra-annular, *mm* millimeters, *LVOT* left ventricular outflow tract anchor and a valve, both retrievable. The frame is 31Fr-profile, retrievable, and contains three porcine pericardial leaflets. Few patients have been treated and an early feasibility study is ongoing [33] which plans to include 20 patients at 5 centers.

The Tendyne system device is a trileaflet porcine pericardial valve in a nitinol frame that is fully retrievable and repositionable. The valve is designed for TA approach, intra-annular positioning and has a ventricular apical fixation system. The largest clinical experience, involving 30 patients, has been with Tendyne system device. The Global Feasibility Study, showed 93.3% of successful implantation, no deaths, strokes or myocardial infarctions. At 30 days, 86.6% were free of cardiovascular mortality, stroke, and device malfunction [34]. Currently an early feasibility trial is looking to enroll 110 patients with severe native MR [35]. The last report with 100 patients at 30 days shows 97% technical success, 6% mortality with most patients having no or trace residual MR [36].

The Twelve Intrepid system (Medtronic, Minneapolis, MN, USA) is a TA self-expanding bovine pericardial bioprosthesis in a nitinol frame (symmetrical). It has an outer fixation ring, designed to fit the variability of the MA, facilitating anchoring through a 'champagne cork' like effect. The latest report of the ongoing pilot study in 50 patients shows 98% successful implantation, with 86% survival and 4% non-disabling stroke at 30 days. The 1-year survival was 76.5% with 79% of patients in NYHA class I or II [36].

Cardiovalve is a transfemoral TSP device with a low profile (28Fr). It is a self-expandable trileaflet bovine pericardial valve that has a robust anchoring and migration forces distribute over 24 focal "sandwiches" points. It also has a robust sealing to prevent paravalvular leak. The first in human implant was performed in December 2017 by our team in Zürich.

The HighLife is either a TA or trans-arterial (for loop placement) device and has two components: a trileaflet bovine pericardial valve and a sub-annular ring to anchor it. In its final position, the native leaflets are trapped between the sub-annular implant and the prosthetic valve. The first report of two cases of HighLife was presented in 2017 [37].

Conclusion

Transcatheter mitral interventions have been developed to address an unmet clinical need and may be an alternative therapeutic option to surgery with the intent to provide symptomatic and prognostic benefit. Beyond MitraClip® therapy, alternative repair technologies are being developed to expand the transcatheter intervention armamentarium. Recently, the feasibility of transcatheter mitral valve implantation in native non-calcified valves has been reported in very high-risk patients. Selection of patients for transcatheter mitral valve repair is complex and requires intimate knowledge of clinical variables and specific device limitations. It is expected that evidence from ongoing trials will not only enable us to refine existing transcatheter mitral valve therapies but also improve clinical outcomes for future patients.

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Carcinoid Heart Disease

51

Anita Nguyen, Hartzell V. Schaff, and Heidi M. Connolly

High Yield Facts

- Carcinoid heart disease affects approximately 20–50% of patients with carcinoid syndrome, which is caused by a malignancy of the neuroendocrine system.
- Cardiac involvement in patients with carcinoid syndrome typically affects the right-sided heart valves.
- Three-year survival of patients with cardiac involvement is estimated to be only 31% compared to 68% in patients with carcinoid syndrome that do not have valvular disease.
- Valve surgery should be considered early after diagnosis of carcinoid heart disease because postoperative survival of patients with NYHA class I–II functional status preoperatively is substantially improved compared to those patients with NYHA class III–IV status.
- Patients with carcinoid heart disease have limited life expectancy, and therefore bioprostheses rather than mechanical valves are preferred for most patients.
- In earlier reports, operative mortality was high (35–63%) for patients with carcinoid heart disease, and these operative deaths were largely due to postoperative bleeding and heart failure.
- In recent series, surgical mortality rates of 5–10% have been reported.
- Overall survival is dependent on the location of the primary tumor, histological grade, and advanced disease stage.
- Patients with low grade, localized disease have a median survival of more than 10 years, but patients with poorly or undifferentiated tumors and distant metastases have a median survival of only 5 months.

Introduction

Carcinoid heart disease affects approximately 20–50% of patients with carcinoid syndrome, which is caused by a malignancy of the neuroendocrine system. These neuroendocrine tumors usually arise from the terminal ileum or appendix and secrete high levels of serotonin (5-HT) and other vasoactive substances, leading to symptoms of facial flushing, bronchoconstriction, and secretory diarrhea [1].

Cardiac involvement in patients with carcinoid syndrome typically affects the tricuspid and pulmonary valves (Figs. 51.1, 51.2, 51.3, and 51.4), and the resulting valvular regurgitation and right heart failure dramatically reduce survival compared to patients who do not have valvular dysfunction (Fig. 51.5). Three-year survival of patients with cardiac involvement is estimated to be only 31% compared to 68% in patients with carcinoid syndrome that do not have valvular disease [2]. Symptoms resulting from heart failure further reduce quality of life for these patients. Surgery for valve replacement can dramatically improve functional status and prevent death due to cardiovascular causes. In selected patients, operation may be recommended to reduce perioperative risk of partial hepatectomy or liver transplantation for hepatic metastases [3, 4].

This chapter provides an overview of evaluation and surgical management of patients with carcinoid heart disease as

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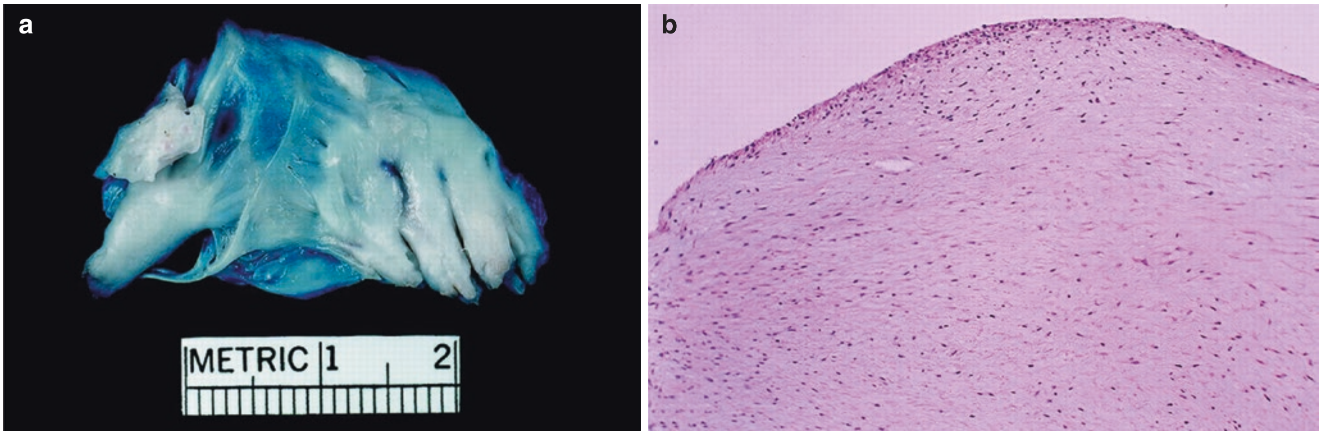

Fig. 51.1 Panel (**a**) shows the anterior mitral valve leaflet of a patient with carcinoid heart disease, which was removed at surgery. This patient had severe mitral valve regurgitation. Leaflet and chordal thickening can also be seen. Panel (**b**) shows microscopic examination; proliferation of myofibroblasts in loose myxoid matrix can be seen. (Copyrighted and used with permission from American Heart Association, Inc. [7])

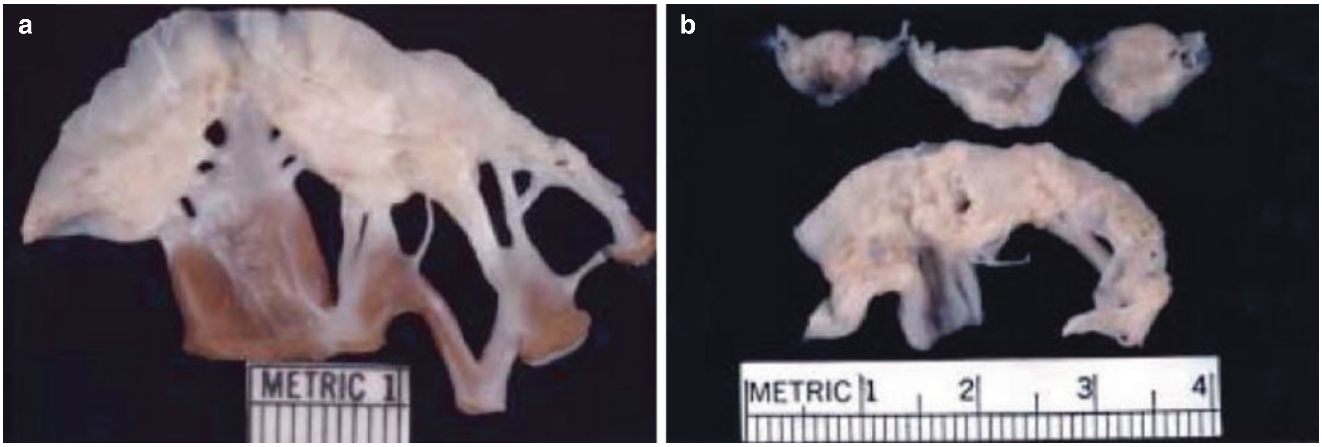

Fig. 51.2 Gross surgical pathologic specimens of carcinoid heart valves. Panel (**a**) shows the tricuspid valve in a patient with severe regurgitation. Panel (**b**) shows the tricuspid and pulmonary valves. (Copyrighted and used with permission from Mayo Foundation for Medical Education and Research [8])

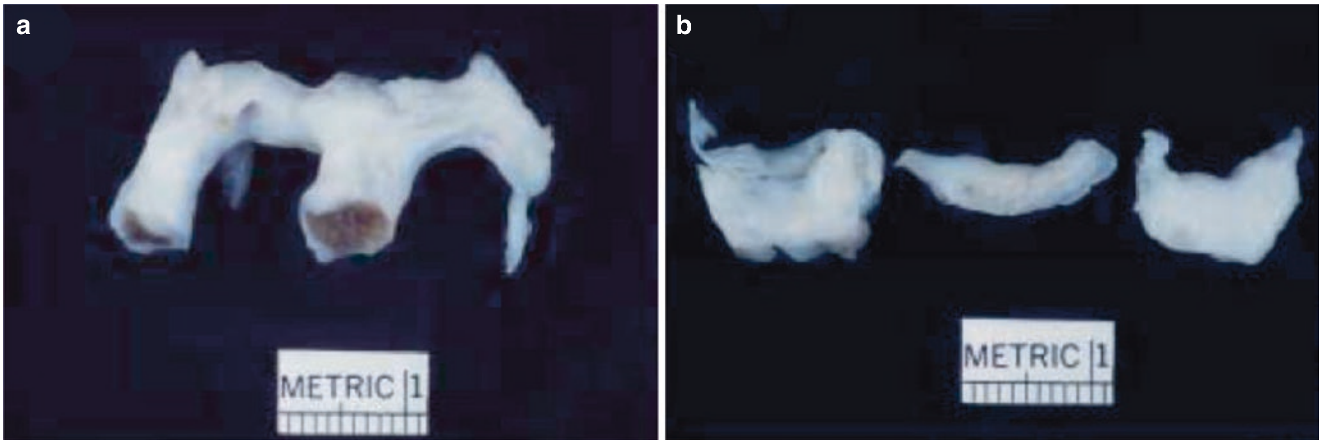

Fig. 51.3 Gross surgical pathologic specimens of carcinoid heart valves from a patient with quadruple valve involvement. Panel (**a**) shows the tricuspid valve, which was stenotic with severe valve regurgitation. Panel (**b**) shows the pulmonary valve. Panel (**c**) depicts the mitral valve. Panel (**d**) shows two of the aortic valve cusps. (Copyrighted and used with permission from Mayo Foundation for Medical Education and Research [8])

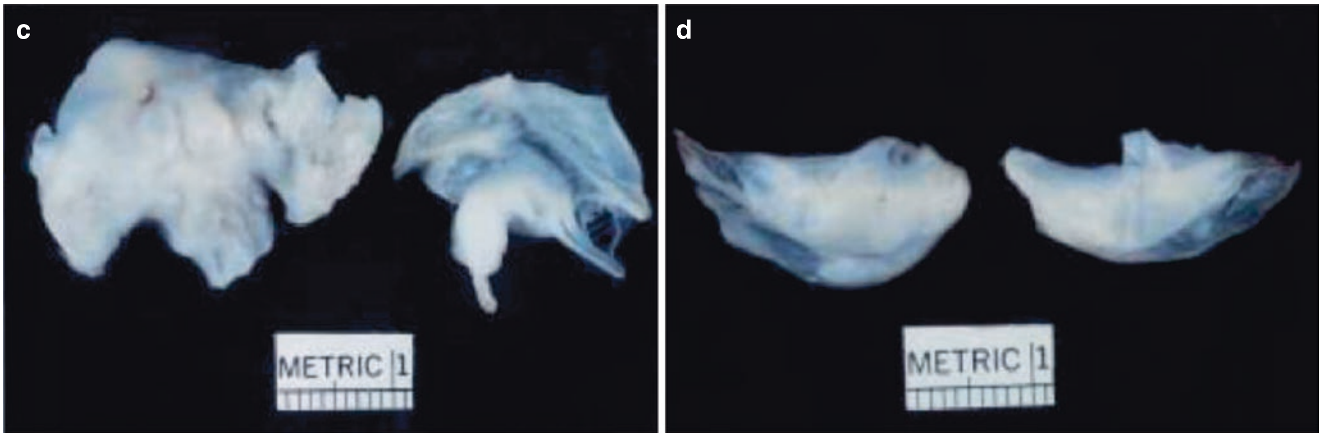

Fig. 51.3 (continued)

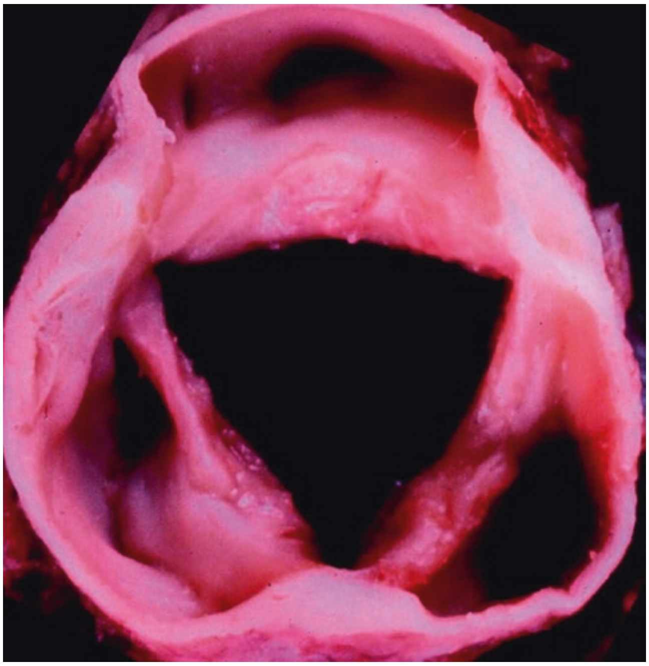

Fig. 51.4 Pathologic specimen showing the pulmonary valve of a patient with carcinoid heart disease. The valve cusps are thickened and immobile, leading to severe pulmonary regurgitation and moderate pulmonary stenosis. (Copyrighted and used with permission from International Anesthesia Research Society [28])

well as further details of early and late outcomes of valve replacement in these patients.

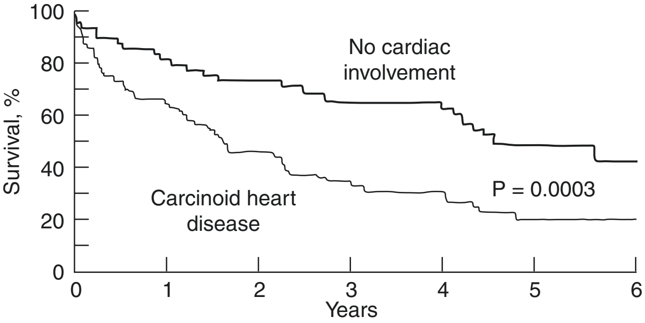

Fig. 51.5 Survival of patients with carcinoid syndrome but no cardiac involvement vs. patients with carcinoid syndrome and cardiac involvement. (Copyrighted and used with permission from American Heart Association, Inc. [2])

Pathology and Pathophysiology

Carcinoid tumors usually arise from the terminal ileum and appendix, and symptoms of flushing and diarrhea develop when hepatic metastases or primary tumors drain directly into the venous circulation or when hepatic inactivation of 5-HT is exceeded. Most patients with carcinoid syndrome have liver metastases, and the vasoactive substances reach the systemic circulation via the hepatic veins. Approximately 5% of patients present with carcinoid syndrome without liver metastases. In patients with primary ovarian carcinoid tumors, vasoactive substances drain directly into the systemic veins bypassing the portal circulation, and this is true for patients with bronchopulmonary tumors, as well as those with retroperitoneal metastases [5, 6].

Carcinoid heart disease occurs in approximately 20–50% of patients with carcinoid syndrome and usually involves the tricuspid and pulmonary valves. It is thought that the lungs inactivate 5-HT leading to lower concentrations of serotonin reaching the left side of the heart. Nevertheless, mitral and/or aortic valves are also affected in approximately 10% of patients. This may occur in patients with atrial septal defects or patent foramen ovale or in patients in whom 5-HT levels are very high and inactivation by the lungs is insufficient [7].

Carcinoid valve disease is caused by carcinoid plaque which results in both thickening and retraction of valve tissue. Thickening is due to cellular proliferation and deposition of extracellular matrix. The tendinous cords of the tricuspid and mitral valves are thickened and focally fused with mild commissural fusion similar to rheumatic valves [8]. Carcinoid involvement of the atrioventricular valves restricts leaflet closure producing valvular regurgitation while stenosis is rarely more than mild.

In vitro studies have demonstrated that serotonin increases proliferation of valvular subendocardial cells in a dose-dependent manner, and this mitogenic effect is inhibited by methiotepin but not ketanserin, suggesting that the mechanism is mediated by 5-HT1b receptors. In human carcinoid heart valves the level of cell proliferation is 35-fold higher than in normal human valves. Further, 5-HT1b receptors are found only in the carcinoid valves, and not in the normal valves. Other serotonin valve receptors, including 5-HT2b, may also be implicated in carcinoid heart disease [9, 10].

Clinical Presentation and Indications for Surgery

Patients with carcinoid heart disease have tricuspid valve regurgitation and some degree of pulmonary valve regurgitation, leading to right-sided heart failure; common symptoms include dyspnea and effort intolerance, and peripheral edema and ascites are often present. The constellation of clinical findings of right heart failure, however, can be confused with symptoms from hepatic disease and tumor progression. Therefore, echocardiographic studies are recommended for all patients with carcinoid syndrome and high suspicion of carcinoid heart disease, such as those with clinical features, murmur, elevated venous pressure or increased NT-proBNP and/or 5-HIAA levels. For patients with established carcinoid heart disease, echocardiography should be performed every 6–12 months or when there is any change in clinical status [1]. Echocardiographic features of carcinoid heart disease are listed in Table 51.1 and illustrated in Figs. 51.6 and 51.7.

Table 51.1 Echocardiographic features of carcinoid heart disease[a]

Tricuspid valve	Thickening of the valve leaflets and subvalvular apparatus Diminished normal concave curvature of the leaflets Altered dynamic motion of the leaflets during diastole Fused and shortened chordae Retraction and reduced excursion of the valve leaflets Tricuspid regurgitation, ranging from mild to severe
Pulmonary valve	Diffusely thickened valve cusps Straightening of cusps Fixed, retracted, and thickened cusps Pulmonary regurgitation and/or (annular) stenosis
Aortic valve	Diffusely thickened valve cusps Straightening of cusps Fixed, retracted, and thickened cusps Pulmonary regurgitation and/or (annular) stenosis
Mitral valve	Diffusely thickened valve cusps Straightening of cusps Fixed, retracted, and thickened cusps Pulmonary regurgitation and/or (annular) stenosis
Right atrium	Dilated
Right ventricle	Dilated Reduced function
Metastases	Location, number, size, and relationship of cardiac metastases to surrounding structures Liver metastases can also be visualized

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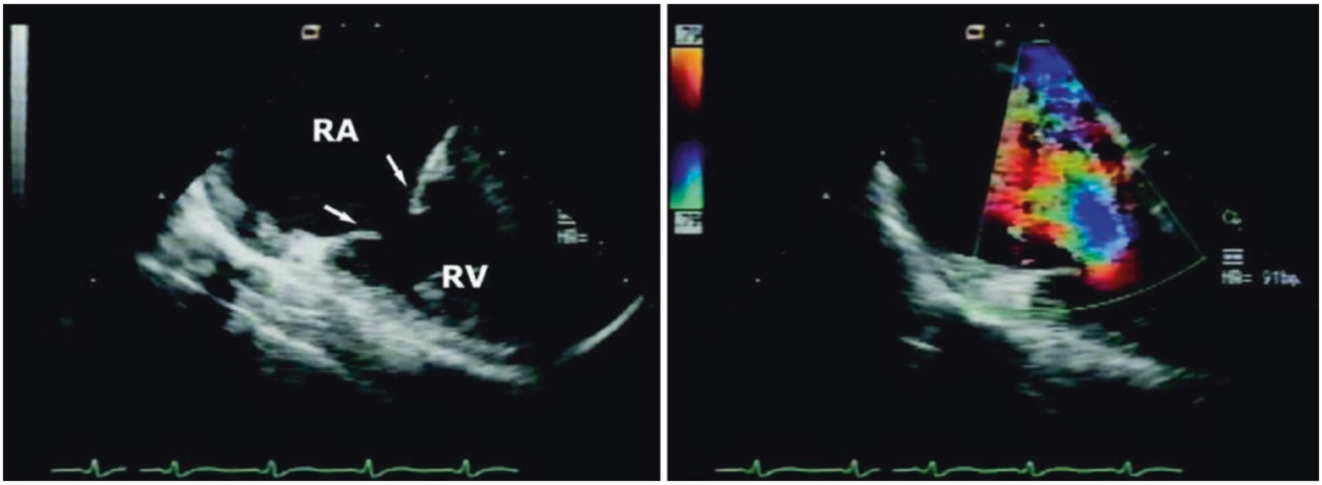


Fig. 51.6 Panel on the left shows the transesophageal echocardiogram of a patient with severe tricuspid valve regurgitation due to carcinoid heart disease. Arrows depict lack of coaptation of the septal and anterior leaflets of the tricuspid valve during systole. *RA* right atrium, *RV* right ventricle. Panel on the right is the same view with Doppler color flow. (Copyrighted and used with permission from International Anesthesia Research Society [28])

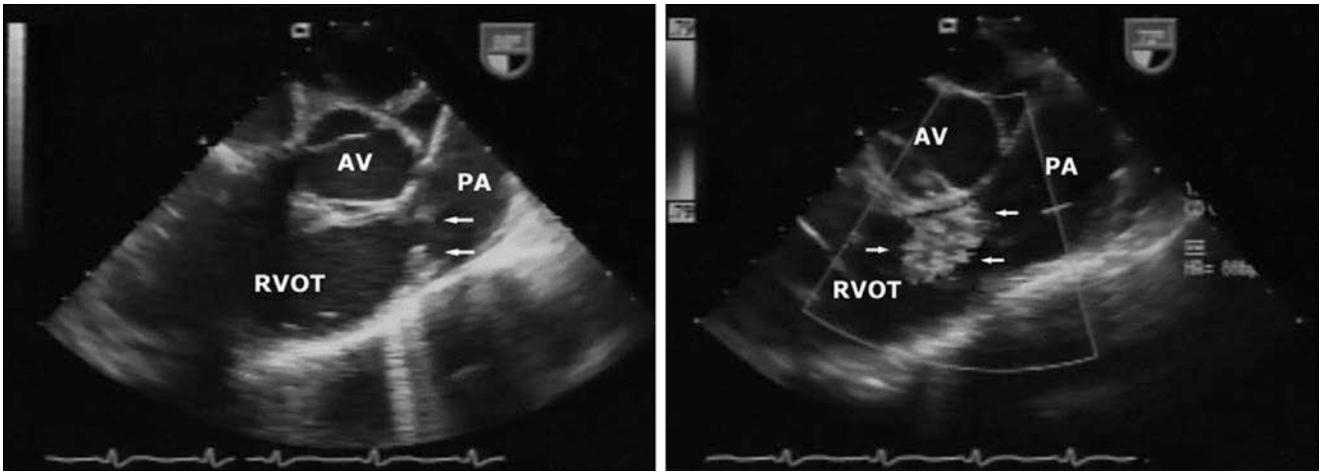


Fig. 51.7 Panel on the left shows the transesophageal echocardiogram of a patient with pulmonary valve disease due to carcinoid heart disease. Arrows depict thickening of the pulmonary valve cusps. Panel on the right shows pulmonary valve regurgitation (arrows). *AV* aortic valve, *PA* pulmonary artery, *RVOT* right ventricular outflow tract. (Copyrighted and used with permission from International Anesthesia Research Society [28])

When echocardiography confirms advanced valve disease in patients with carcinoid syndrome and right heart failure, symptoms related to edema and ascites can be improved with diuretic therapy. But for most patients, improvement with medical treatment is temporary and valve replacement should be discussed. Valve replacement in patients with carcinoid heart disease relieves symptoms, enhances functional status, and may improve survival. Connolly et al. reported that 2-year survival of surgically treated patients with carcinoid heart disease was 40% compared to 8% survival of unoperated patients with carcinoid heart disease [11]. In a more recent study of 200 patients with carcinoid heart disease, Moller and associates found that performance of cardiac surgery was associated with significantly improved survival (hazard ratio 0.44) compared to patients who received medical treatment only [12]. Further, valve surgery should be considered early after diagnosis of carcinoid heart disease because postoperative survival of patients with New York Heart Association (NYHA) class I–II functional status preoperatively is substantially improved compared to those patients with NYHA class III–IV status (Figs. 51.8 and 51.9) [12].

In some patients with severe tricuspid and pulmonary valve regurgitation, valve replacement may be indicated to allow more aggressive treatment of hepatic metastases [3, 13]. It is particularly important to relieve right heart failure before hepatic resection. Marked elevation of right atrial pressure from tricuspid and pulmonary valve insufficiency is directly transmitted to the liver through the hepatic veins and in patients with severe carcinoid heart disease results in a pulsatile liver. Surgery on the liver in this setting leads to substantial and sometimes life-threatening hemorrhage. These risks are mitigated by valve surgery, and a report by Lillegard and coworkers demonstrated that survival of patients who underwent valve replacement followed by hepatic resection was similar to survival of patients without carcinoid heart disease who underwent hepatic resection [3].

Perioperative Management

Careful perioperative management is critical for patients with carcinoid heart disease, and it is particularly important to avoid triggering a carcinoid crisis, which can be exacerbated by general anesthesia. A carcinoid crisis is characterized by labile blood pressure, bronchoconstriction, tachycardia, and flushing. Preoperatively, somatostatin analog therapy with long-acting somatostatins is used to prevent carcinoid crisis during surgery. In patients whose symptoms are not controlled well using these medications, preoperative admission to hospital and intravenous infusion of somatostatins may be necessary. At operation, intravenous somatostatins are administered to all patients. If a patient experiences signs and symptoms suggestive of a carcinoid crisis, additional intravenous boluses of 1000 μg of octreotide should be given. Continuous intravenous octreotide infusion is administered during the early postoperative period, and slowly weaned once the patient is stable [1, 14].

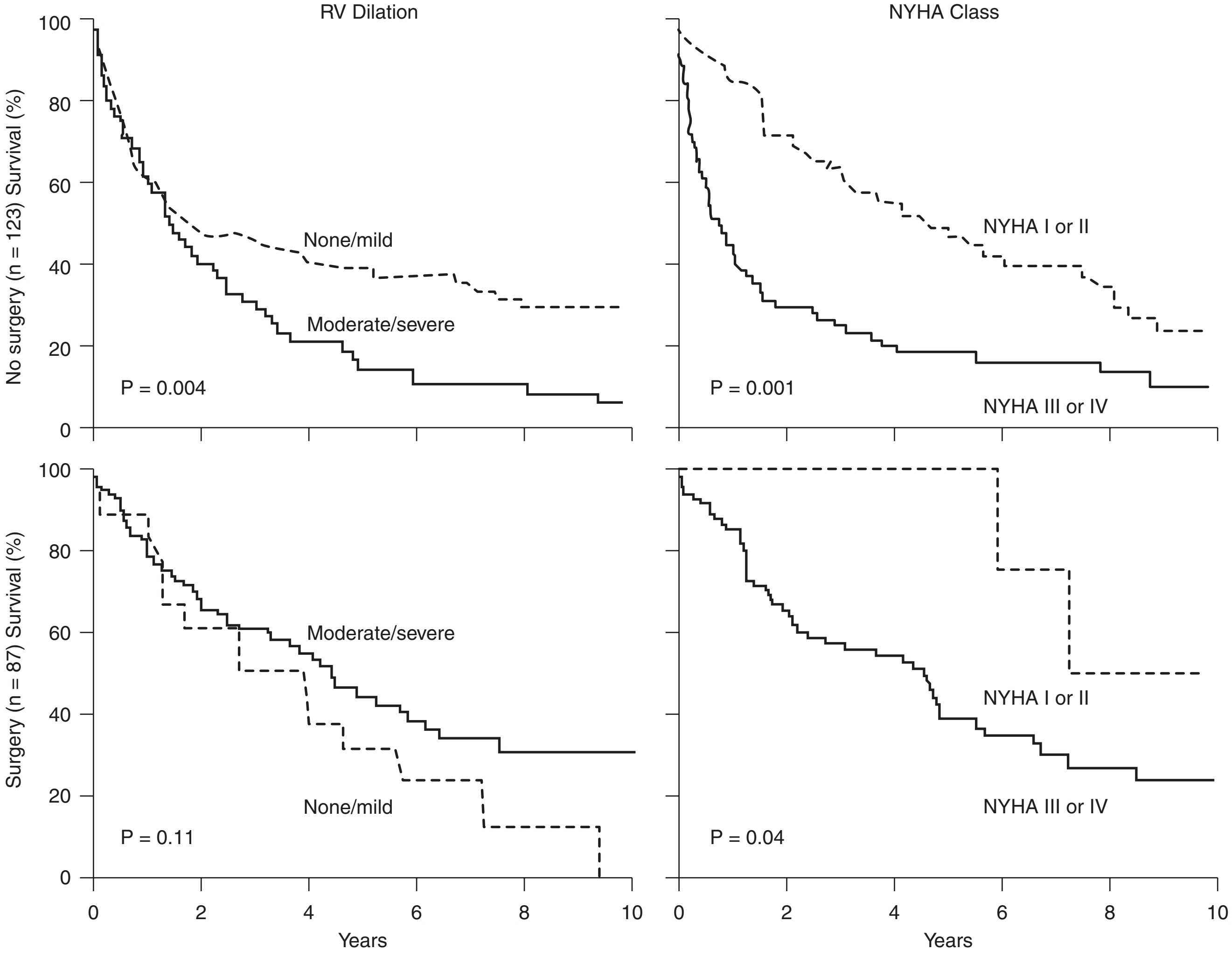


Fig. 51.8 Effects of right ventricular dilation and NYHA class on survival. Top panels show patients who did not undergo surgery. Bottom panels show patients who underwent valve replacement surgery. (Copyrighted and used with permission from American Heart Association, Inc. [12])

Fig. 51.9 Survival of 240 patients with carcinoid heart disease who underwent valve replacement at Mayo Clinic. Panel (**a**) shows overall survival and Panel (**b**) shows survival stratified by preoperative NYHA class. (Copyrighted and used with permission from The American Association for Thoracic Surgery [27])

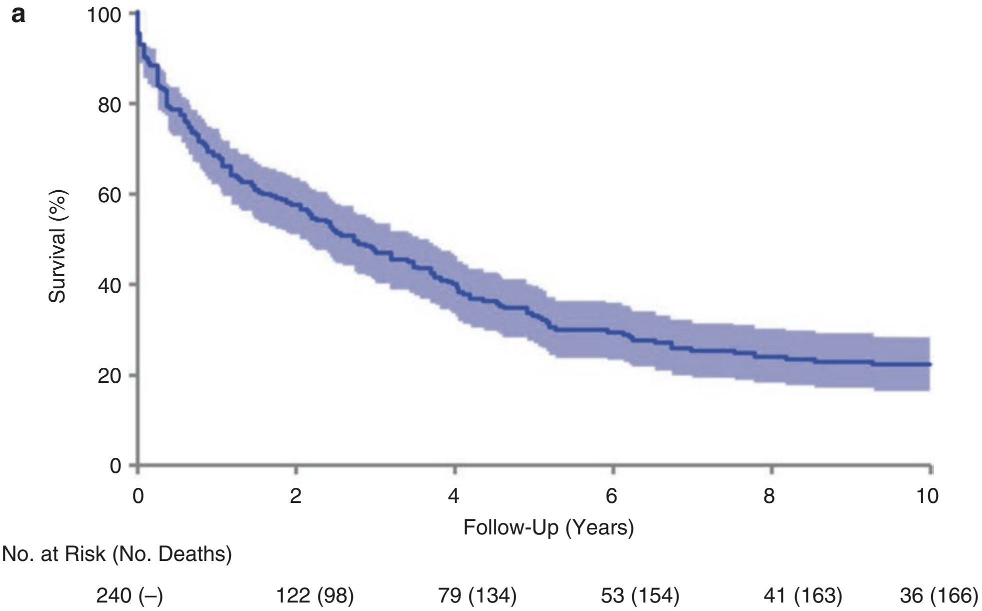
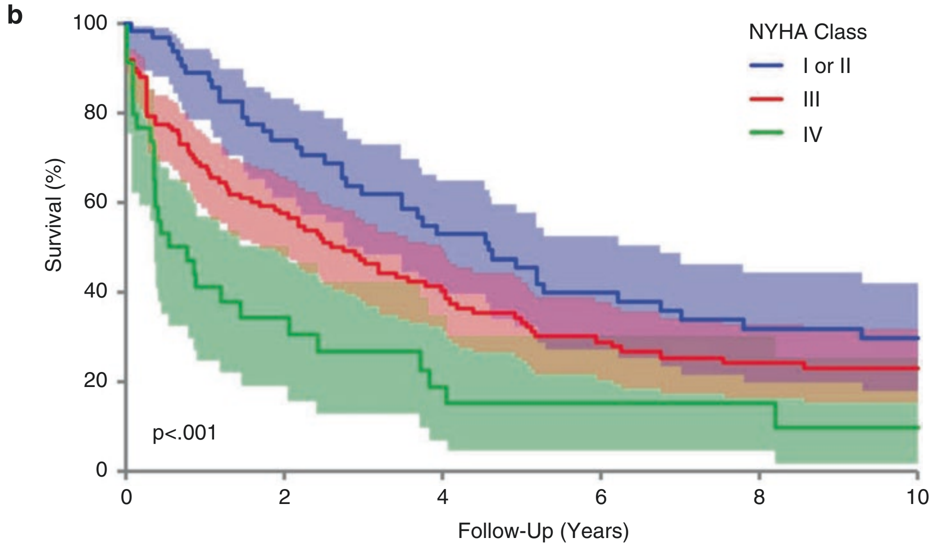


Fig. 51.9 (continued)



No. at Risk (No. Deaths)

🟦	66 (–)	43 (16)	29 (28)	21 (35)	16 (39)	13 (40)
🟥	122 (–)	64 (50)	41 (68)	26 (79)	20 (83)	19 (84)
🟩	35 (–)	9 (22)	5 (26)	3 (27)	3 (27)	2 (28)

Surgical Considerations

Operative Approach

Most patients with carcinoid heart disease have severe tricuspid valve regurgitation and thus, the tricuspid valve is replaced in most instances. Our technique of tricuspid valve replacement involves bicaval cannulation for cardiopulmonary bypass. The heart is arrested with cold blood cardioplegia. We isolate the right atrium and incise it longitudinally. We then inspect the septum for any atrial septal defect or patent foramen ovale, which is closed at the time. The anterior and posterior leaflets of the tricuspid valve are resected, and the annulus is sized. We then place valve sutures (pledget reinforced 2–0 Ethibond) through the tricuspid leaflet remnants with the heart arrested to avoid conduction tissue. The aortic cross-clamp is released, sinus rhythm is restored, and the remainder of the procedure is performed with the heart beating.

In our earlier experience of surgically managing patients with carcinoid heart disease, we routinely excised the pulmonary valve to relieve any degree of stenosis. The resulting pulmonary valve regurgitation was tolerated well in the early postoperative period, but long-term follow-up of these patients has demonstrated increased risk of right ventricular enlargement [15]. Therefore, it has been our practice to replace the pulmonary valve in patients with severe regurgitation. To perform pulmonary valve replacement, we incise the pulmonary artery approximately 3–4 cm distal to the valve annulus. This incision is carried across the valve onto the right ventricular outflow tract. The cusps of the pulmonary valve are excised, and a large pericardial patch is sewn into the pulmonary arteriotomy. The valve prosthesis is sized appropriately and secured to the native annulus posteriorly and the pericardial patch anteriorly. The remainder of the pericardial patch is used to close the ventriculotomy.

Choice of Prosthetic Valves

Patients with carcinoid heart disease have limited life expectancy, and therefore bioprostheses rather than mechanical valves are preferred for most patients. However, outcomes including survival and freedom from intervention are similar following valve replacement with either type of prosthesis [13]. Although tissue valves are usually associated with low risk of thromboembolic complications, thrombotic complications do occur [16]. Valve thrombosis is most likely to occur in the months immediately after surgery and thus, we recommend anticoagulation with warfarin for 3–6 months for patients receiving bioprostheses. For patients with mechanical valves or those with atrial fibrillation, anticoagulation is administered indefinitely.

There is also concern regarding carcinoid recurrence as a cause of bioprosthetic valve dysfunction, which has occurred in <2% of patients in our experience, and is usually seen several years after operation. Thus, there should be a high level of suspicion for thrombosis when bioprosthetic valve dysfunction develops early postoperatively, and a trial of systemic anticoagulation or thrombolysis may be indicated [17].

Left-Sided Heart Disease

Although carcinoid heart disease most commonly affects the tricuspid and pulmonary valves, left-sided heart valve involvement does occur and is commonly thought to result from right-to-left shunting of blood through an atrial septal defect or patent foramen ovale. However, Connolly et al. reported that 55% of patients with left-sided carcinoid valvulopathy confirmed by pathologic examination did not have a defect of the atrial septum [7]. Left-sided disease may also occur in patients with high tumor burden or those with bronchopulmonary carcinoid disease [18, 19]. Replacement of the involved aortic and/or mitral valve should be performed at the same time as tricuspid valve replacement. In rare cases, carcinoid disease can affect all four cardiac valves, and quadruple valve replacement has been performed with good early outcome (Fig. 51.10) [20].

Postoperative Surveillance

A transthoracic echocardiogram is performed in all patients before dismissal from hospital for baseline assessment of prosthetic valve function and hemodynamics. All patients are anticoagulated with warfarin which is continued for 3–6 months for patients who receive a tissue prosthesis and indefinitely for patients with a mechanical valve. Patients who have undergone valve replacement should continue follow-up surveillance with an experienced team specializing in care of patients with carcinoid heart disease. Most clinicians recommend echocardiographic surveillance every 6–12 months, depending on complexity of valve disease and other patient comorbidities [1].

Outcomes of Valve Replacement for Carcinoid Heart Disease

Perioperative Mortality

In earlier reports, operative mortality was high (35–63%) for patients with carcinoid heart disease, and these operative deaths were largely due to postoperative bleeding and heart failure [11, 18, 21]. However, with advances in surgical techniques, perioperative care, and improved experience, operative mortality rates have decreased; in recent series, surgical mortality rates of 5–10% have been reported [13, 22–24]. At our Clinic, early operative mortality has decreased from 20% for patients who underwent operation before 1990 to 4% for those who had surgery since 2010 (Fig. 51.11) [13]. Indeed, early operative mortality for patients with carcinoid heart disease, who commonly require double valve replacement, is similar to that of adult cardiac patients undergoing multiple valve surgery to treat other valve pathologies [25].

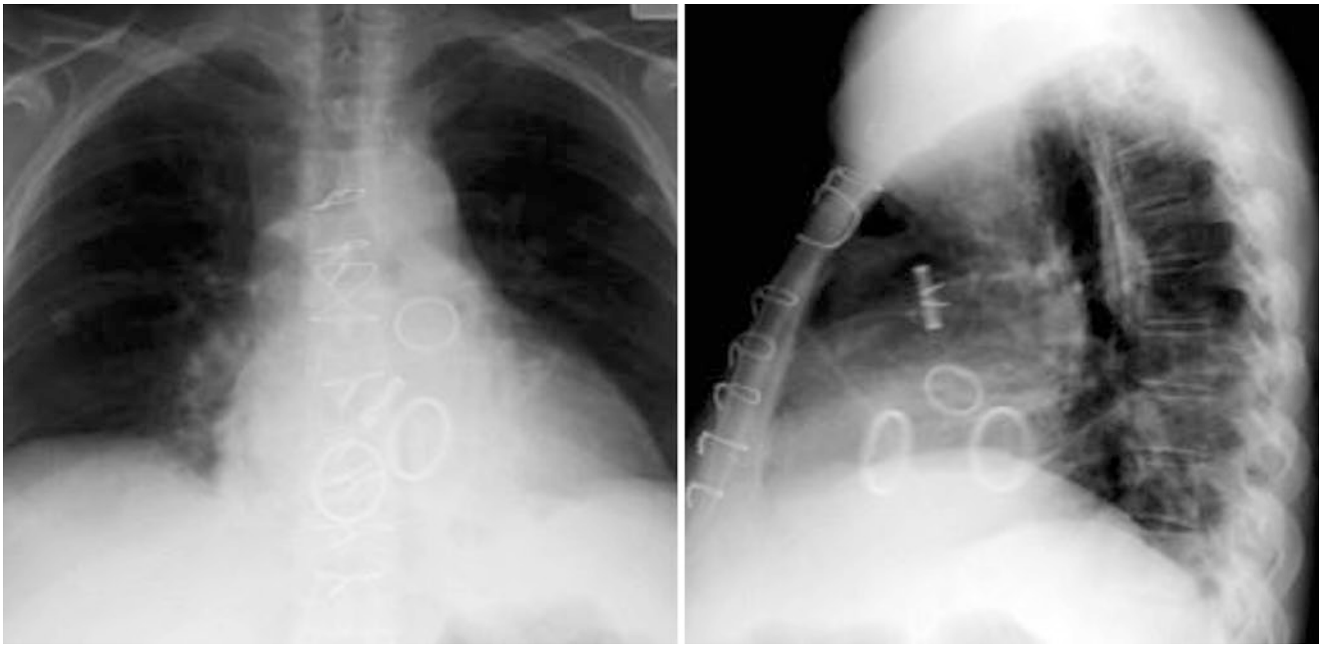


Fig. 51.10 Chest radiographs showing the posteroanterior and lateral views of a patient with carcinoid heart disease following quadruple valve replacement. (Copyrighted and used with permission from The American Association for Thoracic Surgery [20])

Overall Survival and Functional Outcomes

Despite improvement in operative mortality, valve replacement for carcinoid heart disease is still associated with relatively high late mortality, and this is mainly caused by tumor and disease progression. Overall survival is dependent on the location of the primary tumor, histological grade, and advanced disease stage. Patients with low grade, localized disease have a median survival of more than 10 years, but patients with poorly differentiated or undifferentiated tumors and distant metastases have a median survival of only 5 months [18, 26].

At Mayo Clinic, more than 200 patients with carcinoid valve disease have undergone cardiac valve replacement [27]. Although overall survival was limited by tumor progression, patients with lower NYHA class preoperatively had better outcomes compared to patients who were in NYHA class III or IV before operation (Fig. 51.9). Furthermore, risk of late reoperation was low in our cohort of patients, and only 16 patients required reintervention on a cardiac valve (Fig. 51.12). Importantly, patients experienced excellent improvement of heart failure symptoms during early follow-up (Fig. 51.13). Thus, although overall survival is limited, symptoms from heart failure can be significantly improved in patients with carcinoid heart disease who have successful valve replacement.

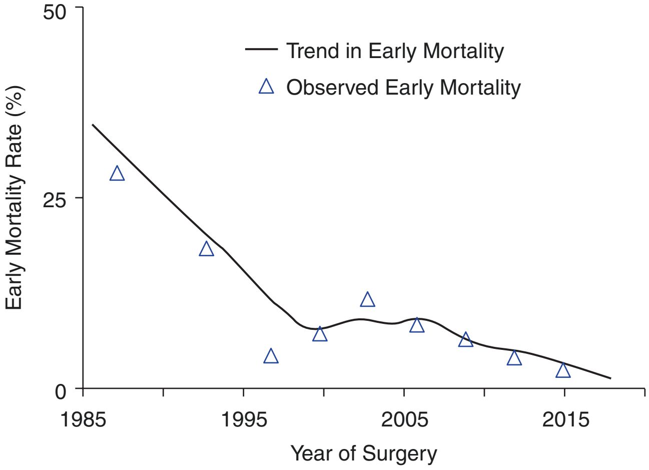


Fig. 51.11 Early operative mortality (<30 days following surgery) among 240 patients with carcinoid heart disease who underwent valve replacement at Mayo Clinic. (Copyrighted and used with permission from The American Association for Thoracic Surgery [27])

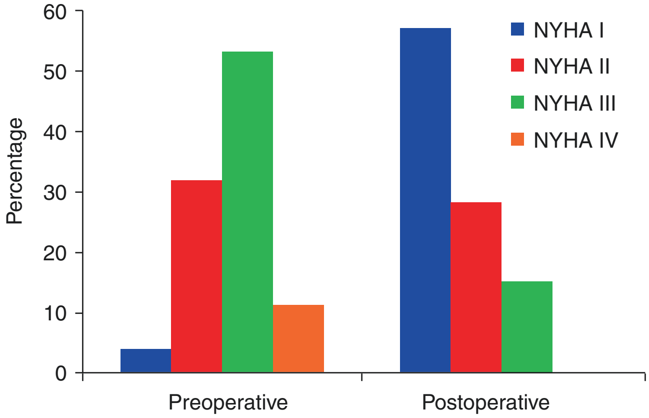
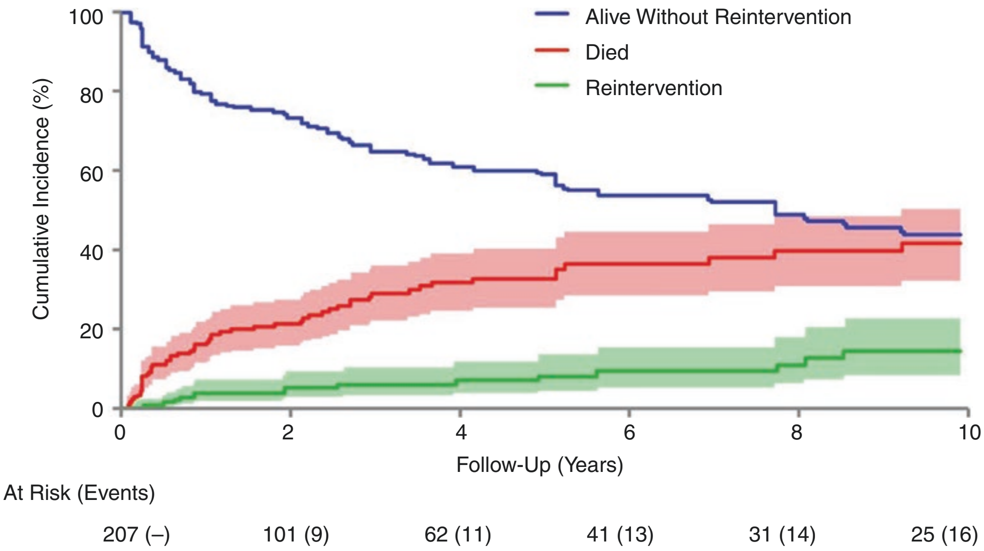


Fig. 51.13 Functional outcomes of 107 patients who underwent valve replacement surgery at Mayo Clinic. Median follow-up time was 0.5 (0.3, 0.9) years following operation. (Copyrighted and used with permission from The American Association for Thoracic Surgery [27])

Fig. 51.12 Risk of cardiac valve reintervention of 240 patients with carcinoid heart disease who underwent valve replacement at Mayo Clinic. (Copyrighted and used with permission from The American Association for Thoracic Surgery [27])



Conclusion

Carcinoid heart disease is characterized by fibrosis of heart valves, which mainly affects the tricuspid and pulmonary valves. Care of patients with carcinoid heart disease should be based on a multi-disciplinary approach at experienced centers. For patients who have severe tricuspid valve regurgitation, valve replacement has excellent short-term survival and functional outcomes, especially for those who have operation before developing advanced symptoms. Bioprosthetic valves are safe for patients with carcinoid heart disease, and late occurrence of carcinoid valvulopathy or valve thrombosis is infrequent.

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Part IV

Thoracic Aorta

52

Acute Type A Aortic Dissection

Alice Le Huu, Umang M. Parikh, and Joseph S. Coselli

High Yield Facts

- Aortic dissection divides the aorta into two channels: the true lumen and the false lumen.
- Aortic dissections are classified and managed by anatomical involvement and chronicity.
- Stanford type A aortic dissection indicates the involvement of the ascending aorta.
- Acute type A aortic dissection (ATAAD) is a dangerous condition; in patients without intervention, 50% do not survive beyond 48 h of onset.
- The gold standard treatment for ATAAD is open proximal aortic repair. Although endovascular approaches are being developed, substantial barriers exist, including the fragility of aortic tissue in ATAAD.
- The clinical presentation of ATAAD often involves the acute onset of sharp chest pain, occasionally with syncope or malperfusion, and it can be mistaken for myocardial infarction. Branching arteries can arise from either channel, and related malperfusion is not uncommon.
- Although ATAAD is challenging to diagnose on the basis of patient-reported symptoms, it can be readily identified by using computed tomography or transesophageal echocardiography.
- ATAAD may be additionally classified as DeBakey type I or II aortic dissection. DeBakey type II dissection is limited to the aortic root and ascending aorta and does not extend into the transverse aortic arch. DeBakey type I aortic dissection is extensive and commonly extends from the proximal aorta to the iliac bifurcation.
- Controversy surrounds the treatment of more extensive (e.g., DeBakey type I) ATAAD. Some centers prefer to use a limited approach to focus on enhancing early survival, and other centers prefer to use an extended approach to reduce late aortic dilation in the residual chronically dissected native aorta.
- Most ATAAD patients require lifelong hypertension control and surveillance imaging.

Introduction

Acute type A aortic dissection (ATAAD) is a life-threatening condition affecting the proximal aorta (i.e., the aortic root, ascending aorta, and aortic arch), often necessitating emergent care. Without treatment, approximately 50% of patients with an ATAAD do not survive beyond 48 h [1]. Even if a patient receives medical care, the prognosis of patients with ATAAD remains dismal; many patients die soon after arriving to the hospital, and the rate of mortality after surgical repair is substantial [2–4].

ATAAD represents a formidable clinical entity because it occurs relatively rarely and is difficult to diagnose. ATAAD is the most common acute aortic syndrome, with an incidence of 3–4 cases per 100,000 individuals [5]; consequently, physicians are likely to encounter this disease within their practice. However, considering the elevated mortality rate associated with ATAAD, and because these deaths are potentially preventable, a missed diagnosis of ATAAD can be catastrophic.

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The open repair of ATAAD has dramatically altered the natural history of the disease, resulting in a contemporary mortality rate of 18% for patients treated surgically compared with 57% for patients treated medically [2]. Although this decreased mortality rate in ATAAD patients treated surgically is partially attributed to improved operative management, it is also attributed to increased awareness and early detection of ATAAD, a greater understanding of the pathophysiology of the disease, and improved surgical expertise. Therefore, a thorough understanding of all these factors will contribute to optimal patient outcomes.

Clinical Presentation

Patients with ATAAD classically present with sharp chest pain radiating to the back. These symptoms are often mistaken for myocardial infarction—a far more prevalent condition. Furthermore, ST-segment elevation due to an aortic dissection extending into the coronary arteries and related malperfusion can blur the line between a myocardial infarction and an ATAAD. A physician must remain vigilant when encountering a patient with chest pain, especially if the patient is relatively young, to correctly identify ATAAD.

ATAAD affects a wide range of age groups, including extremes at either end of the age spectrum, but most aortic dissections tend to occur in men over the age of 60 [6]. Other findings common to patients experiencing ATAAD are symptoms of malperfusion (Fig. 52.1), including cardiac tamponade, heart failure due to aortic valve regurgitation, coronary artery ischemia, focal neurologic symptoms, renal complications, ischemic limbs with pulse deficits, and hypotension. A multitude of risk factors have been established for the development of ATAAD and should be considered when making a diagnosis. Between 70% and 85% of patients with a dissection have a pre-existing diagnosis of hypertension. Other conditions commonly present in patients experiencing ATAAD include atherosclerosis (24%), known aortic aneurysm (13%), prior aortic dissection (4%), or prior cardiac surgery (16%) [6]. Iatrogenic risk factors of ATAAD include catheter-based interventions and represent an unfortunate consequence of medical procedures.

Patients can be predisposed to aortic dissection by heritable thoracic aortic diseases such as Marfan syndrome, which is the most well known [7, 8]. Loeys-Dietz syndrome is a lesser known condition but arguably places patients at a greater risk of aortic dissection and at smaller aortic diameters. Additionally, patients with bicuspid aortic valves appear to be at greater risk of aortic dissection; however, prophylactic repair of the proximal aorta in patients with bicuspid aortic valves remains controversial.

Diagnostic Testing

The gold standard imaging modality for the diagnosis of ATAAD is computed tomography angiography (CTA) (Fig. 52.2). A computed tomography angiogram quickly demonstrates the presence of a dissection flap and allows for visualizing the extent of the dissection and identifying potential areas of malperfusion. CTA is fast, sensitive, and available at most medical centers. If CTA is contraindicated because of contrast-induced allergy or renal disease, transesophageal echocardiography (TEE) or transthoracic echocardiography (TTE) can alternatively be used. The sensitivity and specificity of TEE and TTE for the diagnosis of ATAAD are highly dependent on operator experience, as well as the echogenicity of the patient. However, with TEE, the entire thoracic aorta or the coronary arteries cannot be imaged [9]. Although intraoperative TEE is not ideal for the initial diagnosis of ATAAD, it is indispensable for determining the extent of aortic valve regurgitation, thus guiding operative decision making. Immediately after surgery, TEE also can be used to determine the competency of the repaired aortic valve and the success of a repair. A third imaging modality, magnetic resonance imaging (MRI), is likely to provide clinicians with information similar to that provided by CTA. However, MRI has not been widely used to diagnose ATAAD because of lack of access and availability.

In contemporary practice, ATAAD cannot be diagnosed on the basis of laboratory test results. However, in recent years, the D-dimer protein and its role in screening for dissection has been of interest to researchers [10]. Recent data showed that the D-dimer protein is sensitive to acute aortic syndromes, and normal levels of D-dimer protein suggest the absence of ATAAD. Currently, efforts are under way to develop an acute aortic dissection risk score (ADD-RS) + D-dimer score for use as a screening tool to rule out aortic dissection. Previously, the ADD-RS was developed and validated by the International Registry of Acute Dissections (IRAD) and was primarily based on high-risk features related to the patient's condition, exam, and pain characteristics. Integration of the ADD-RS with D-dimer tests can rule out dissection with 97% sensitivity [11].

Pathology and Classification

The presence of risk factors associated with the development of ATAAD can vary among patients, but the mechanism of injury is similar. Classic aortic dissection occurs with the formation of a tear in the intimal layer of the aorta. Blood flows under pulsatile pressure through the medial layer, propagating a longitudinal cleavage between the two layers

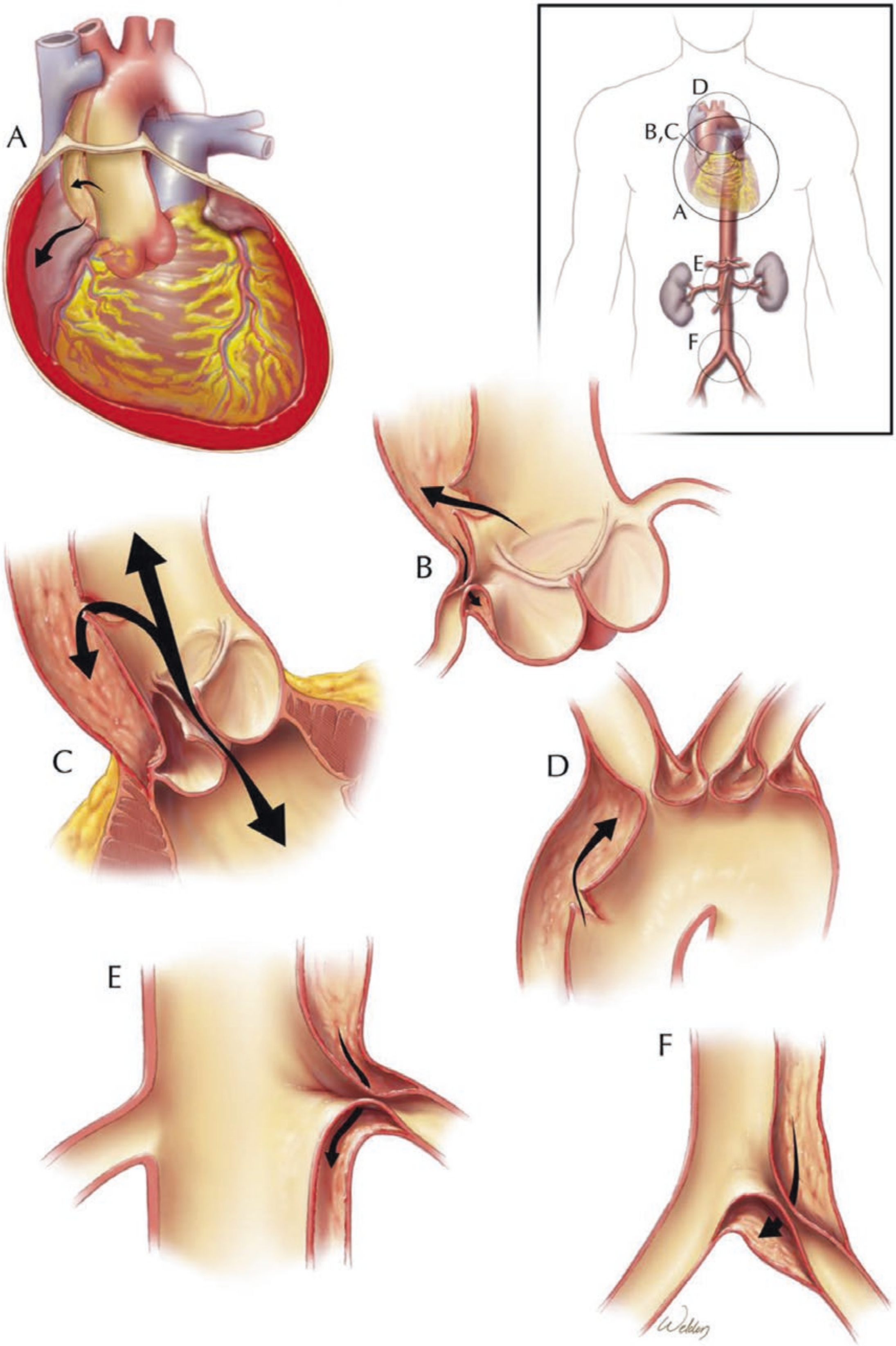

Fig. 52.1 Illustration of the potential anatomic consequences of aortic dissection—several regions may be affected (inset). (**a**) Cardiac tamponade and rupture of the ascending aorta. (**b**) Malperfusion of coronary arteries. (**c**) Aortic valve regurgitation, caused by injury. Compromised blood flow to the (**d**) brachiocephalic, (**e**) renal, and (**f**) iliac arteries. (Used with permission of Baylor College of Medicine)

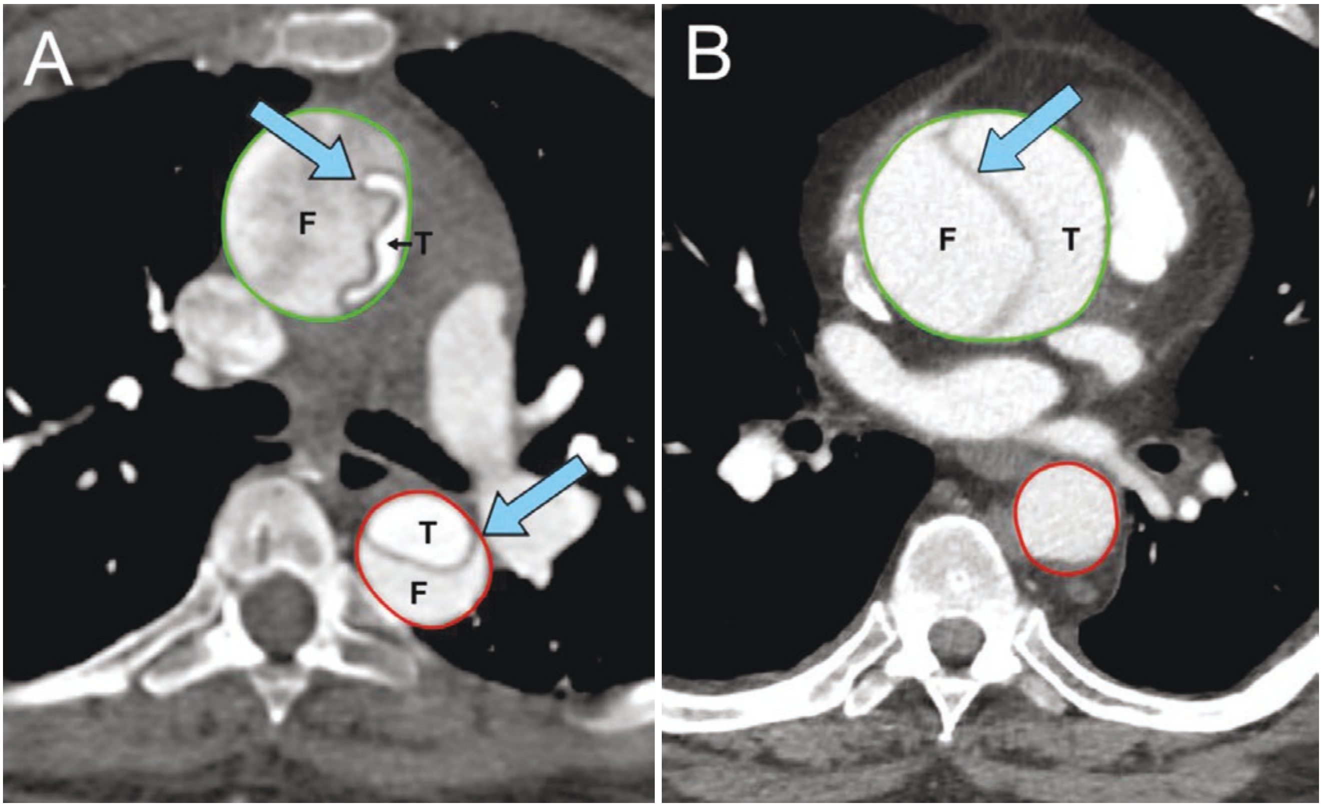

Fig. 52.2 Computed tomography scans of acute proximal aortic dissection showing a DeBakey type I aortic dissection (**a**) contrasted against a DeBakey type II aortic dissection (**b**). In the patient with type I, the true lumen (T) has been almost completely compressed by the false lumen (F) in the proximal aorta (within the green circle); however, in the distal aorta (within the red circle), the lumens are approximately equal in size. In the patient with type II, a true (T) and false (F) lumen are visible in the proximal aorta (within the green circle), but there is no dissection of the distal aorta (within the red circle). (Used with permission of Baylor College of Medicine)

and creating a false lumen. This competing channel of blood flow can extend the length of the aorta and often compresses the true lumen. For ATAAD, the origin of the tear is usually in the ascending aorta, and the dissection commonly travels in an antegrade direction. Secondary re-entry tears in the dissecting membrane permit additional communication between the true and false lumen.

Variants of aortic dissection include intramural hematoma and penetrating aortic ulcer, which are treated like ATAAD (Fig. 52.3). An intramural hematoma can result from the spontaneous rupture of the vasa vasorum (e.g., without an intimal tear or communication with the aortic lumen), but it may evolve into a more traditional aortic dissection [12, 13]. A penetrating aortic ulcer is a disrupted atherosclerotic plaque that has eroded through the intima into the vasa vasorum and may lead to rupture or dissection. When intramural hematomas and penetrating aortic ulcers are discovered in the ascending aorta, patients are referred for surgery; however, the urgency is typically somewhat less than that of a classic ATAAD.

Notably, ATAAD may propagate in a retrograde fashion; a dissection such as this is commonly termed a retrograde type A dissection (RTAD). An RTAD occurs when the intimal tear of an ATAAD originates beyond the left subclavian artery and travels into the ascending aorta in a retrograde manner [14]. RTAD may occur spontaneously, but it may alternatively result from a complication of thoracic endovascular aortic repair (TEVAR). RTAD after TEVAR has an incidence between 1.3% and 6.8% [15] and is an iatrogenic complication that is believed to be caused by excessive ballooning of the proximal end of the stent graft, oversizing of the prosthesis, stent configuration, or a fragile aorta [16]. RTAD is usually managed the same as ATAAD; however, reports in the literature have emerged of conservative medical management in very small numbers [17, 18]. The rationale for this is that the tear is in a retrograde direction while aortic blood flows in the antegrade direction; therefore, an RTAD may be self limiting.

Aortic dissection can be categorized by using either the Stanford or DeBakey methods of classification (Fig. 52.4) [19, 20]. Appropriate designation of the type, severity, and extent of ATAAD is essential to determine treatment and prognosis. However, it is important to note that neither of these systems considers the origin of the intimal tear, which can influence

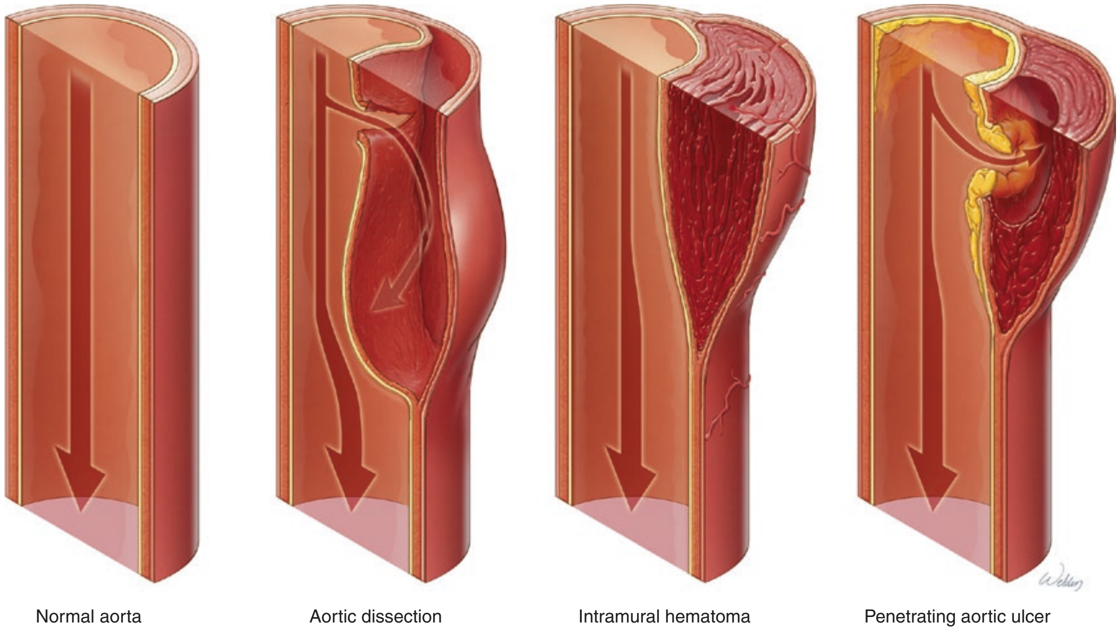
Normal aorta
Aortic dissection
Intramural hematoma
Penetrating aortic ulcer

Fig. 52.3 Illustration of longitudinal sections of the aortic wall and lumen. Blood flows freely downstream in normal aortic tissue. In classic aortic dissection, blood enters the media through a tear and creates a false lumen within the aortic wall. Variants of classic aortic dissection include intramural hematoma and penetrating aortic ulcer; for all, the outer aortic wall is compromised and prone to rupture. Intramural hematoma involves a hemorrhage from the vasa vasorum that causes blood to collect within the media; however, the innermost layer of the aortic wall (the intima) remains intact. Penetrating aortic ulcers are atherosclerotic lesions that burrow into the aortic wall and allow blood to enter the media. (Used with permission of Baylor College of Medicine)

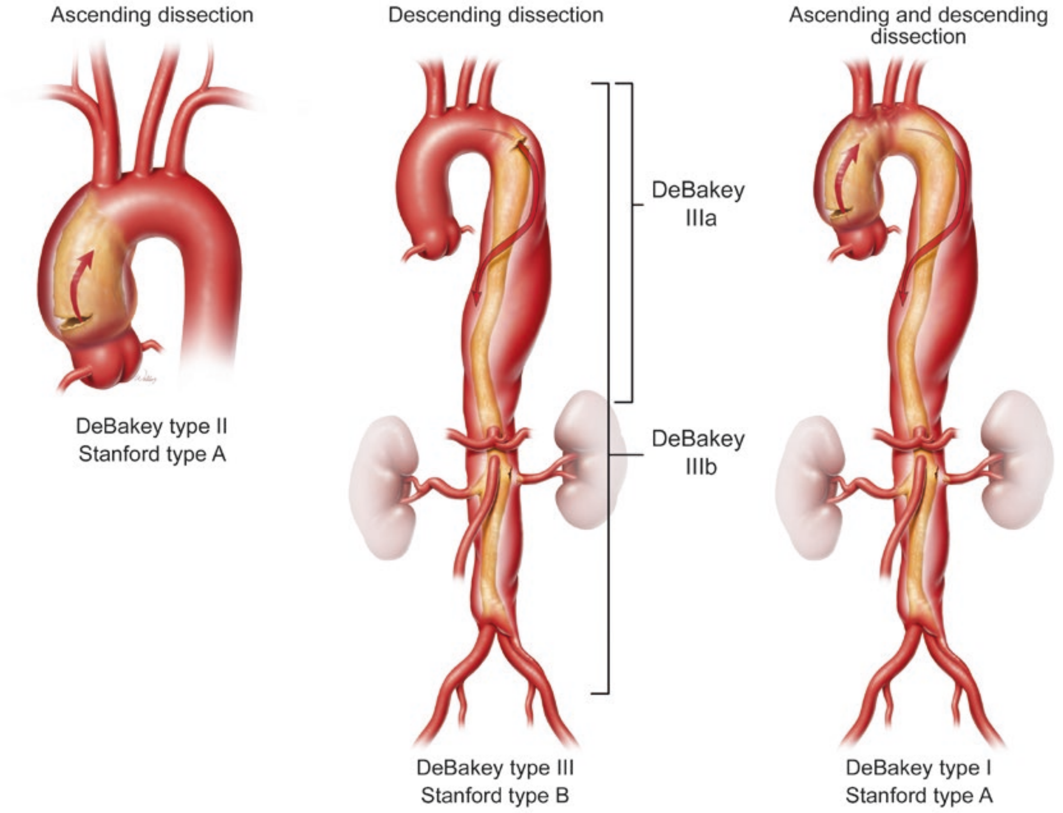
Ascending dissection
Descending dissection
Ascending and descending dissection
DeBakey IIIa
DeBakey IIIb
DeBakey type II
Stanford type A
DeBakey type III
Stanford type B
DeBakey type I
Stanford type A

Fig. 52.4 Illustration of the DeBakey and Stanford classification schemas for acute aortic dissection. Dissection of the proximal aorta may be limited to the ascending aorta or it may extend distally to the aortic bifurcation. (Used with permission of Baylor College of Medicine)

surgical management. DeBakey's original classification of proximal aortic dissection includes two distinct types, as follows: type I dissection originates in the ascending aorta and propagates into the arch and the varying portions of the distal aorta (i.e., the descending thoracic and thoracoabdominal aorta); and type II dissection originates in and is confined to the ascending aorta [20]. The original classification stipulates that a DeBakey type II dissection ends proximal to the origin of the innominate artery; however, in practice, an ATAAD often extends into the aortic arch. Although an ATAAD involving the arch without extension past the left subclavian artery is commonly considered a DeBakey type II aortic dissection, it does not strictly meet the original criteria of a DeBakey type II aortic dissection [21]. In contrast to the DeBakey classification system, the Stanford system proposes that an aortic dissection be classified as type A or type B. Type A includes all dissections involving the ascending aorta, regardless of origin; type B includes all dissections that do not involve the ascending aorta [19]. It is important to note that neither the DeBakey nor Stanford classification system accounts for isolated dissections of the aortic arch, which are relatively rare.

Aortic dissections are further categorized as acute or chronic, depending on the time elapsed after the initial tear. Traditionally, aortic dissections have been considered acute if the symptomatology suggests that the sentinel event occurred within 14 days. Beyond that time frame, the dissection is treated as a chronic entity. The IRAD further delineates the chronicity of aortic dissection into the four following categories: hyperacute (within 24 h), acute (2–7 days), subacute (8–30 days), or chronic (>30 days) [22]. Defining the precise onset of the dissection has important implications for the urgency of the operation, surgical planning, and prognosis.

Surgical Technique

Patients who are diagnosed with ATAAD and are operative candidates undergo expedited emergency surgical repair. Hypothermic circulatory arrest (HCA) with antegrade cerebral perfusion (ACP) is commonly used during the repair of ATAAD. In addition, the anesthesia team uses standard monitoring techniques including near-infrared spectroscopy to measure cerebral oxygen saturation and right and left radial arterial lines. Standard venous inflow is established through a two-stage cannula in the right atrium. A ventricular vent is placed via the right superior pulmonary vein. For myocardial protection, a retrograde cardioplegia perfusion catheter is routinely placed via the right atrium into the coronary sinus. In our practice, we typically provide the patient with bilateral ACP to protect both hemispheres of the brain, although unilateral ACP remains an acceptable approach at many centers. In the hemodynamically stable patient, arterial inflow for cardiopulmonary bypass (CPB) is established via a balloon perfusion catheter placed inside a graft that is sewn end-to-side to either the right axillary artery or the innominate artery. The innominate artery is used only if CTA and direct examination findings indicate that the dissection does not extend into this vessel. Perfusion into the innominate artery, either directly or via the axillary artery, allows the right common carotid artery and right vertebral artery to be perfused when the proximal innominate artery is controlled. In the presence of hemodynamic instability, the rapid initiation of CPB through the femoral vessels is an option. Additional cannulation sites may be used, including the direct cannulation of the ascending aorta or aortic arch; in this case, transesophageal echocardiography can be used to confirm that the cannula is located within the true lumen.

Table 52.1 Categories of hypothermia established by an expert consensus (Adapted from Ref. [30])

Category of hypothermia	Nasopharyngeal temperature, °C
Profound	<14
Deep	14.1–20
Moderate	20.1–28
Mild	28.1–34

Once CPB has commenced, we systemically cool the patient to a moderate target temperature of 24 °C (nasopharyngeal); at some centers, depending on the complexity of the operation, the patient may be cooled to a lower target temperature (e.g., in the case of a total arch replacement with elephant trunk extension) (Table 52.1). In recent years, the widespread use of ACP has permitted warmer patient temperatures during ATAAD repair. We believe that bilateral ACP should be used routinely, but its use is especially important in complex cases necessitating prolonged cerebral perfusion times. This is done by inserting a 9-French balloon perfusion catheter directly into the left common carotid artery. Once the target temperature is reached, the origin of the innominate artery is clamped, and CPB flows are maintained at 1.0–1.5 L/min [23]. Because the ascending aorta and aortic root are opened, we routinely provide additional cardioplegia by directly infusing the coronary arteries with the use of handheld perfusion cannulas. Once satisfactory cerebral and myocardial protection has been established, the full extent of the dissection and its pathology must be examined and confirmed. Surgical options are discussed below; a summary of these options is provided in Table 52.2.

Arch Repair Options

The primary goal of any intervention for ATAAD is patient survival. Repair of the arch may be limited to graft replacement of the lesser curvature of the arch (i.e., a hemiarch repair), or it may involve graft replacement of the entire transverse aortic arch (i.e., a total arch repair). In many circumstances, a limited hemiarch and ascending aortic repair is performed (Fig. 52.5), having a much lower risk of death

Table 52.2 Common repair strategies for acute type A aortic dissection, by section

Aortic arch	Aortic root	Extension into distal arch or descending thoracic aorta
• Hemiarch vs. total arch replacement • Majority of cases proceed with hemiarch approach • Total arch approach is usually reserved for cases in which the arch is dilated more than 4.5–5 cm or the tear involves the arch	• Aortic valve commissural resuspension vs. aortic root replacement vs. non-root replacement of the aortic valve and ascending aorta • Generally, a conservative approach to resuspend the aortic valve is the first choice in many centers • Non-root replacement of the aortic valve and ascending aorta leaves the coronary arteries intact; this may be helpful in select patients • ARR techniques include the following: – CVG using mechanical or bioprosthetic valves – Valve-sparing	• Extensive aortic dissection or dilatation present • Total aortic arch replacement may be extended with an elephant trunk graft; in a subsequent completion repair, an open or endovascular repair of the distal aorta is performed • Total aortic arch replacement may incorporate a distal endograft; this is termed a frozen elephant trunk repair; it is an experimental approach that is not yet FDA approved • Hemiarch approach may be combined with antegrade TEVAR

ARR aortic root replacement, *CVG* composite valve graft, *FDA* Food and Drug Administration, *TEVAR* thoracic endovascular aortic repair

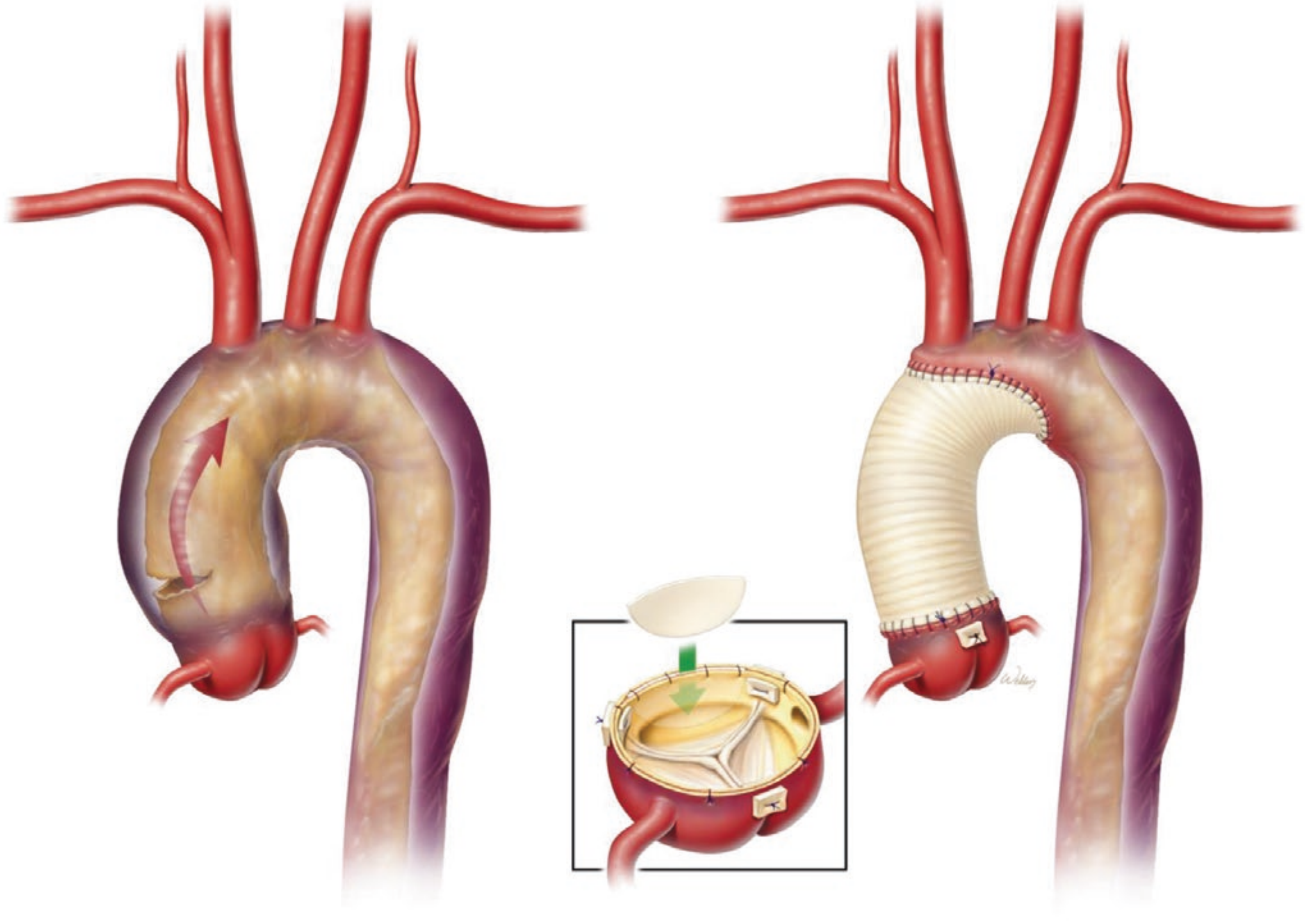

Fig. 52.5 Illustration of a limited approach to repair in a case involving acute proximal aortic dissection. (**a**) The originating tear is shown above the sinutubular junction in a case involving DeBakey type I aortic dissection. During resuspension of the aortic valve, a tongue of Teflon is added to support the noncoronary sinus (inset). (**b**) Replacement of the ascending aorta and hemiarch is shown. (Used with permission of Baylor College of Medicine)

or stroke than a total replacement of the transverse aortic arch. A caveat of this approach is that total arch replacement may decrease the need for a future reoperation [24, 25]. In experienced centers with a high volume of aortic cases, a full arch and elephant trunk reconstruction in the setting of ATAAD may be performed, with acceptable morbidity and mortality rates. However, anatomic constraints may make total arch replacement virtually unavoidable. Examples include acute dissection superimposed on a grossly dilated transverse aortic arch and the presence of multiple primary and re-entry tears extensively throughout the arch.

Once the aorta has been drained of blood, the full extent of the dissection is revealed. In both a hemiarch and total arch repair, preparation of the open distal anastomosis is the same: the true and false lumens are opened, and the thrombus between them is removed. The circumference of the true and false lumens is reapproximated with felt strips or pericardium for reinforcement of the friable tissue. If a hemiarch is planned, then a straight graft is selected. In the case of a total arch repair, the technique selected for re-implantation of the branching arteries of the arch will dictate the type of graft selected. Brachiocephalic vessels may be reattached as an island or replaced with a branched graft (e.g., by using an anatomically based branched graft or a Y-graft approach that reroutes the brachiocephalic vessels). Typically, in young patients with heritable thoracic aortic disease, individual re-implantation of the brachiocephalic vessels is favored to eliminate as much abnormal tissue as possible. In both a hemiarch and a total arch repair, the anastomosis between the Dacron graft and aorta is completed with running 4–0 polypropylene sutures; in addition, a collared graft is commonly used to facilitate any discrepancy in diameter. The posterior aspect of the anastomosis is typically reinforced with additional pledgeted sutures, either from the inside or on the exterior of the graft.

Aortic Root Repair Options

Once the distal anastomosis has been completed, the aortic root and valve are evaluated. When the dissection does not extend into the root and the valve leaflets are normal, commissural resuspension of the aortic valve may be sufficient. If the valve leaflets are fused or have fenestrations or calcifications, an option is to perform an aortic valve replacement combined with a supracoronary graft replacement of the ascending aorta. Previously, BioGlue has been used to help reapproximate the true and false lumens and to obliterate the space between them; however, concerns regarding the toxicity of BioGlue have led to a decline in its use. To add support during the resuspension of the aortic valve, a tongue of Teflon may be placed within the dissected layers of the noncoronary sinus of the aortic root (Fig. 52.5). It should be noted that the conservative management of the root leaves the sinuses of Valsalva intact; therefore, these patients may require additional interventions in the future.

Aortic root repair may be necessary in the presence of a grossly dissected aortic root, a dilated sinotubular junction >4.5 cm, a known heritable thoracic aortic disease, or other risk factors. Options for aortic root replacement include either replacing or sparing the native aortic valve. For an aortic root replacement that also replaces the aortic valve, a mechanical valve is commonly used, but a bioprosthetic valve, porcine bioprosthetic root, or homograft may be substituted. Management of the aortic root depends on a combination of patient factors and surgeon expertise; interestingly, in a comparison of conservative root management versus extensive repair, no difference in hospital mortality was observed [26].

Conventional and Frozen Elephant Trunk and Related Techniques

Often, an ATAAD may extend into the distal aorta, such as in a DeBakey type I aortic dissection. Surgeons may choose to address the descending thoracic aorta within the same setting or plan for future interventions. Two methods are commonly used in this situation: the elephant trunk (ET, an open approach) or the frozen elephant trunk (FET, an endovascular approach) [12]. The classic ET usually consists of two separate open repairs that may be separated by weeks to years. The primary goal of the FET is to complete a single-stage repair of the ascending aorta, aortic arch, and descending thoracic aorta by using a hybrid approach involving both open and endovascular techniques.

In the initial stage of a conventional ET repair, the ascending aorta and aortic arch are replaced, and a free-floating inverted extension of the graft is placed in the proximal portion of the descending thoracic aorta. For the completion ET repair, an open descending thoracic or thoracoabdominal aortic repair is performed in which the trunk facilitates the proximal anastomosis. In a hybrid ET approach, the trunk is used as a proximal landing zone for a stent-graft in the subsequent completion of repair. In this case, a retrograde approach is used to deploy an endovascular stent graft inside of the ET, which is an off-label application of TEVAR.

In contrast to traditional or hybrid ET repair, an FET repair is performed in a single stage, commonly by using a hybrid prosthesis that is part graft and part stent-graft. A sewing collar typically separates the graft and endograft and facilitates the distal arch anastomosis, which is completed first. Then, the stent-graft is deployed in the antegrade direction through the sewing collar to repair the proximal portion of the descending thoracic aorta. The remainder of the aortic arch surgery is then completed along with the proximal anastomosis. Because this is an experimental approach, long-term studies are lacking. However, FET approaches are especially useful if distal aortic malperfusion is present. Furthermore, these approaches may remodel limited sections of the distal aortic dissection, thereby reducing the risk of distal aortic repair in the future [27].

An additional approach for extending repair in a single setting is the use of antegrade TEVAR immediately followed by the use of a hemiarch approach (Fig. 52.6). The brachiocephalic arteries are preserved, and the endograft is used to repair a short portion of the descending aorta, thereby "sealing" the distal aortic portion of the aortic dissection. In our experience, we tend to use this approach in patients with malperfusion or with severe compression of the true lumen by the false lumen [28]. As a precaution against migration, we secure the endograft circumferentially with 3–0 pledgeted sutures in the proximal descending thoracic aorta distal to the left subclavian artery, leaving only a small portion of native aortic arch. Unlike traditional hemiarch repair, this hybrid approach obstructs a few pairs of intercostal arteries and creates a potential risk of postoperative paraplegia. With all endovascular extensions into the descending thoracic aorta (e.g., FET, hybrid ET, antegrade TEVAR), the concern of spinal cord ischemia is heightened; therefore, we tend to limit this approach to a single endograft that is either 10 or 15 cm in length.

Complications and Surveillance

Results from our single-practice experience from 1997 to 2018 have shown acceptable overall operative outcomes for patients with ATAAD who underwent a variety of operative approaches, including aortic root and ascending aortic replacement extending into the hemiarch or total arch, performed with or without ET, FET, and hybrid antegrade TEVAR repairs (Table 52.3). Our results show a 12% rate of 30-day death, a 4% rate of persistent stroke, and a 20% rate of adverse events, defined as 30-day death or persisting (present at the time of discharge) stroke, paraplegia, paraparesis, or renal failure necessitating dialysis. Results from contemporary studies of the open repair of ATAAD from different institutions are summarized in Table 52.4 and show similar variability; early mortality rates range from 10.2% to

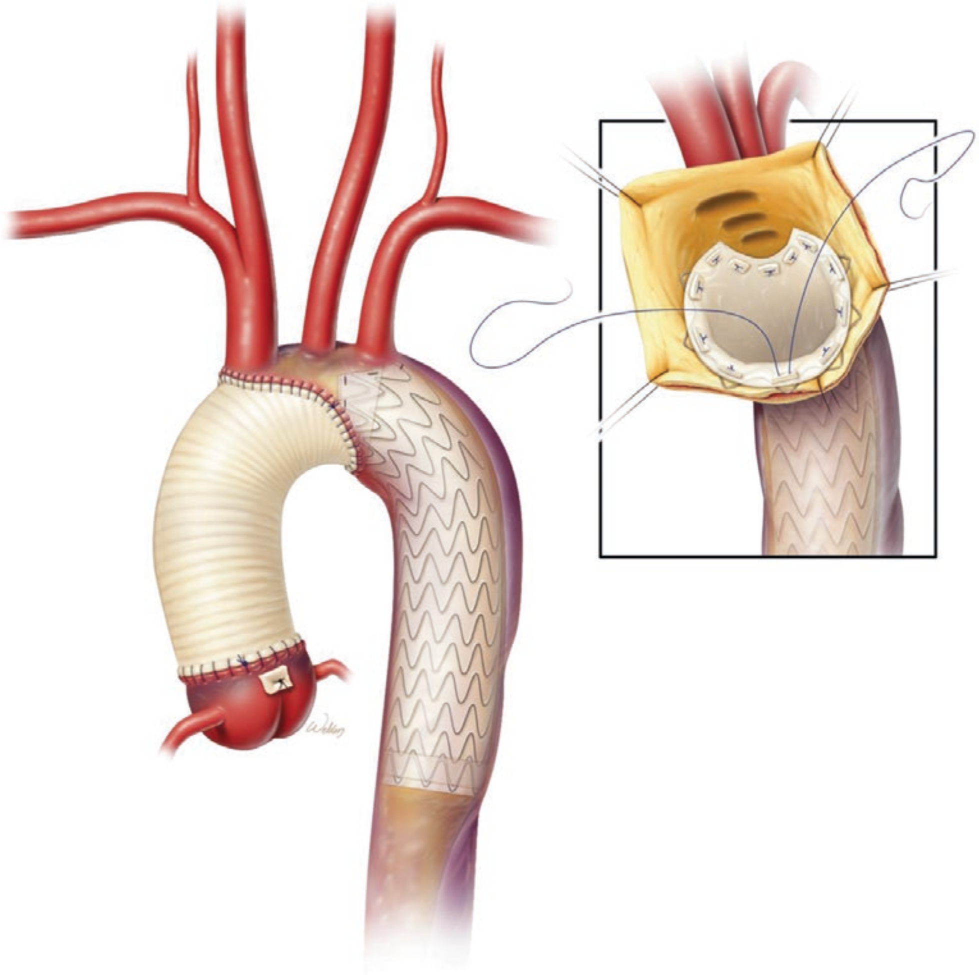

Fig. 52.6 Illustration of a hemiarch repair with antegrade endovascular repair in a case involving acute DeBakey type I aortic dissection and distal malperfusion. A small notch is cut into the endograft to permit blood flow into the left subclavian artery (inset). To reduce the risk of distal endograft migration, the endograft is reinforced with pledgeted sutures circumferentially. (Used with permission of Baylor College of Medicine)

Table 52.3 Preoperative characteristics, operative details, and early outcomes in patients with acute type A aortic dissection who underwent arch repair (1997–2018)

Variable	All (n = 380)	Ascending (n = 377)	Total arch (n = 33)[a]	Hemiarch (n = 347)	Hemiarch + TEVAR (n = 58)
Preoperative characteristics					
Age (years), median [IQR]	62 [50–70]	62 [50–70]	62 [51–71]	62 [50–70]	65 [54–71]
Male	258 (68)	255 (68)	23 (70)	235 (68)	42 (72)
DeBakey type I dissection	330 (87)	327 (87)	31 (94)	299 (86)	57 (98)
DeBakey type II dissection	50 (13)	50 (13)	2 (6)	48 (14)	1 (2)
Hypertension	314 (83)	312 (83)	28 (85)	286 (82)	55 (95)
HTAD	30 (8)	30 (8)	5 (15)	25 (72)	2 (3)
Genetic disorder (HTAD or age ≤ 50 years)	105 (28)	105 (28)	9 (27)	96 (28)	12 (21)
Operative details					
Elective repair	20 (5)	18 (5)	3 (9)	17 (5)	0
Urgent or emergent repair	360 (95)	359 (95)	30 (91)	330 (95)	58 (100)
Redo sternotomy	61 (16)	58 (15)	5 (15)	56 (16)	6 (10)
Aortic root replacement	67 (18)	66 (18)	6 (18)	61 (18)	5 (9)
Aortic valve replacement (without root)	27 (7)	25 (7)	4 (12)	23 (7)	7 (12)
Aortic valve suspension (without root/AVR)	235 (62)	235 (62)	16 (48)	219 (63)	44 (76)
Coronary artery bypass graft	47 (12)	46 (12)	2 (6)	45 (13)	2 (3)
Early outcomes					
Adverse event	75 (20)	75 (20)	5 (15)	70 (20)	11 (19)
30-day death	44 (12)	44 (12)	3 (9)	41 (12)	6 (10)
Persistent stroke	17 (4)	17 (5)	1 (3)	16 (5)	4 (7)
Persistent paraplegia	3 (1)	3 (1)	0	3 (1)	1 (2)
Persistent paraparesis	8 (2)	8 (2)	0	8 (2)	2 (3)
Persistent renal failure necessitating dialysis	35 (9)	35 (9)	1 (3)	34 (9)	6 (10)

Data are presented as a number and percentage (%) unless otherwise indicated

An adverse event comprises 30-day death or persisting (present at the time of discharge) stroke, paraplegia, paraparesis, or renal failure necessitating dialysis

AVR aortic valve replacement, *IQR* interquartile range, *HTAD* heritable thoracic aortic disease, *TEVAR* thoracic endovascular aortic repair

[a] Includes eight cases of elephant trunk extensions, including two frozen elephant trunk extensions

Table 52.4 Summary of contemporary reports regarding the open repair of acute type A aortic dissection

First author	Year published	Experience (years)	Extension into arch	n	Early death (%)	Stroke (%)
Kohl (IRAD data) [31]	2018	2006–2015	None, HAR, TAR, FET	1872	17.1	9.7
Lee (STS data) [32]	2018	2011–2012	None, HAR, TAR, FET	2982	17.4	10.9
Omura [33]	2016	1999–2014	HAR, TAR	197	10.2 (HAR) 14.7 (TAR)	8.3 (HAR) 5.7 (TAR)
Conzelmann (GERAADA data) [34]	2016	2006–2010	None, HAR, TAR, FET	2137	16.9	—
Ganapathi [35]	2014	2005–2013	HAR	440	17.0	2.9

FET frozen elephant trunk, *HAR* hemiarch repair, *GERAADA* German Registry for Acute Aortic Dissection Type A, *IRAD* International Registry of Acute Dissections, *STS* Society for Thoracic Surgeons, *TAR* total arch replacement

17.4%, and stroke rates range from 2.9% to 9.7%. These results are consistent with those achieved at our institution.

Close surveillance of survivors of ATAAD is crucial because of the likelihood that these patients will need additional aortic repair, especially those with extensive residual aortic dissection (e.g., a survivor of acute DeBakey type I aortic dissection). Once a patient is successfully discharged, CTA scans of the chest and abdomen are indicated 4–6 weeks later, at 6 and 12 months, and yearly thereafter. As needed, a more frequent imaging schedule may be followed. The residually dissected aorta tends to dilate over time, especially if the false lumen is patent, which is not uncommon in patients with extensive dissection. Persistent perfusion of the false lumen typically happens in a retrograde fashion but may be caused by secondary entry sites, trauma secondary to aortic cross clamping resulting in a new tear, or a leak in the original anastomosis.

If an isolated ascending or hemiarch repair was performed and residual dissection remained, subsequent repair of the transverse aortic arch may be needed. In addition, patients with residual dissection of the distal aorta (i.e., the descending thoracic or thoracoabdominal aorta) may need subsequent distal aortic repair. Current guidelines suggest that a chronically dissected descending thoracic aorta should be repaired when the diameter exceeds 5.5 cm, the rate of growth is greater than 0.5 cm/year, or symptoms are present [3]. Open repair of a chronic distal aortic dissection may be performed with good to excellent outcomes because the patients tend to be younger and are commonly free of atherosclerotic burden [29].

Conclusion

ATAAD is a rare but catastrophic acute aortic syndrome. Good patient outcomes depend on a prompt diagnosis and urgent surgical intervention. The extent of the repair is dependent on a multitude of factors including patient comorbidities, hemodynamic instability, and surgeon experience. Patients who survive after an ATAAD require close monitoring and optimal medical management. Because it is not uncommon that additional aortic pathologies develop in these patients and may require reoperation, ATAAD patients typically require lifelong surveillance imaging.

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Acute Type B Aortic Dissection

53

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High Yield Facts

- According to Stanford Classification system, type B includes only dissections of the descending aorta beyond the left subclavian artery.
- Acute aortic dissection occurs in 3.5–14 per 100,000 persons per year worldwide.
- Compared with type A dissection, type B dissection occurs more frequently in older patients, black patients, and those with underlying atherosclerosis.
- Approximately 5% of acute aortic dissections are recurrent.
- Recurrent aortic dissection is more frequently found in Marfan patients compared with the general population (21.5% vs. 3.1%).
- Uncomplicated dissections comprise up to 85% of all acute type B dissections in most series.
- First line treatment for uncomplicated type B aortic dissection is beta blockade, also termed “anti-impulse therapy”, with a target systolic blood pressure of 100–120 mmHg and heart rate below 60–70 beats per minute.
- Twenty-five to fifty percent of medically treated patients develop late aortic complications, most commonly aneurysmal degeneration of the false lumen.
- In patients with acute type B dissection with malperfusion or rupture, thoracic endovascular stent grafting has emerged as the standard of care (Class 1 indication, Level of evidence A).
- Open surgery should be reserved for cases where anatomy is inappropriate or for patients with connective tissue disorders.

Introduction

Aortic dissection is the most common aortic emergency and requires prompt diagnosis and often necessitates early surgical intervention. Dissection occurs when an intimal-medial tear occurs, allowing blood to propagate through the outer third of the medial layer, resulting in the formation a false lumen (Fig. 53.1). Over recent years, our understanding of aortic dissection has vastly improved secondary to the establishment of The International Registry of Acute Aortic Dissection (IRAD). IRAD was founded in 1996 and is comprised of a consortium of 30 referral centers in 11 countries [1]. The registry now includes over 3800 acute aortic dissections, and several landmark studies have been performed utilizing this data. Device technology has also rapidly evolved over the past decade, allowing for increased endovascular therapeutic options. This chapter provides an overview and updates on type B aortic dissection (TBAD), which are dissections involving the aorta distal to the left subclavian artery.

Nomenclature

Aortic dissections are categorized based on the anatomic location and acuity. The Stanford classification system, described in 1970, is the most widely used in the literature

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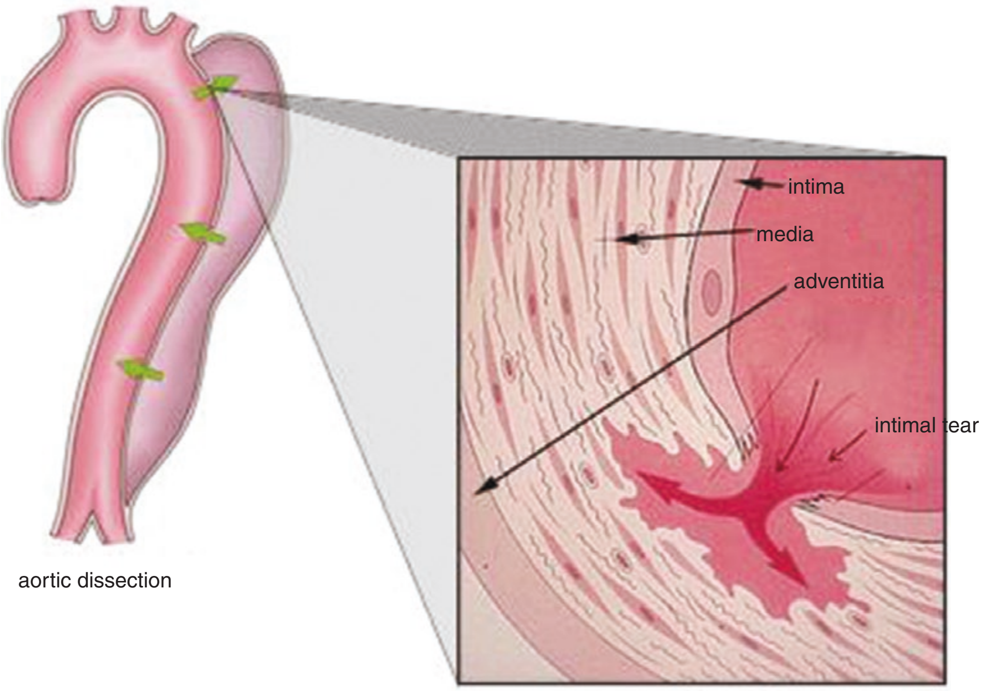

Fig. 53.1 Dissection occurs when an intimal-medial tear occurs allowing blood to propagate through the outer third of the medial layer, resulting in the formation a false lumen

and categorizes dissection simply as Type A or B. Type A includes any dissection involving the ascending aorta, whether or not there is concomitant descending aortic involvement. Type B includes only dissections of the descending aorta beyond the left subclavian artery. The DeBakey classification system, described in 1965, is more detailed and categorizes dissection involving the proximal aorta, arch and descending aorta as DeBakey type I (Stanford type A), the ascending aorta alone as DeBakey type II (Stanford type A), the descending thoracic aorta alone beyond the left subclavian artery as DeBakey type IIIa (Stanford type B), and the descending thoracic and thoracoabdominal aorta as DeBakey type IIIb (Stanford type B) (Fig. 53.2). Of note, neither of current classification systems adequately describes the rarer subset of dissections limited primarily to the aortic arch.

The acuity classification of aortic dissection has evolved, with most recent classifications including acute, subacute, and chronic phases, although the exact temporal classification of these phases varies between systems. We favor the acuity classification put forth by the European Society for Vascular Surgery (ESVS) in which an aortic dissection is categorized as acute within 2 weeks of symptom onset, subacute from 2 weeks to 3 months following symptom onset, and chronic as beyond 3 months from symptom onset [2]. The morphology of the aorta evolves following dissection with the intimal flap thickening and becoming less mobile, along with an increase in aortic wall fibrosis, changes which happen primarily over the first 3 months post-dissection. Acute type B dissections are further classified as complicated or uncomplicated. Complicated type B dissections account for 15–20% of cases and includes patients with clinical malperfusion or rupture. Some would also include refractory pain and/or hypertension as complicated dissections given the high rate of complications in this cohort, although this is not universally agreed upon [3–5].

Demographics, Etiology and Risk Factors

Acute aortic dissection occurs in 3.5–14 per 100,000 persons per year worldwide [6, 7]. Studies from IRAD have identified several risk factors for development of acute aortic dissection [8] (Table 53.1). Compared with type A dissection, type B dissection occurs more frequently in older patients, black patients, and those with underlying atherosclerosis [6, 7]. Recurrent aortic dissection (i.e. newly diagnosed acute on chronic aortic dissection) has become increasingly recognized, likely due to more liberal use of early computed tomography (CT) scanning, improved medical care after initial dissection, and overall increased patient longevity. Recent work from IRAD has demonstrated that approximately 5% of acute aortic dissections are recurrent. Recurrent aortic dissection is more frequently found in Marfan patients compared with the general population (21.5% vs. 3.1%) [9].

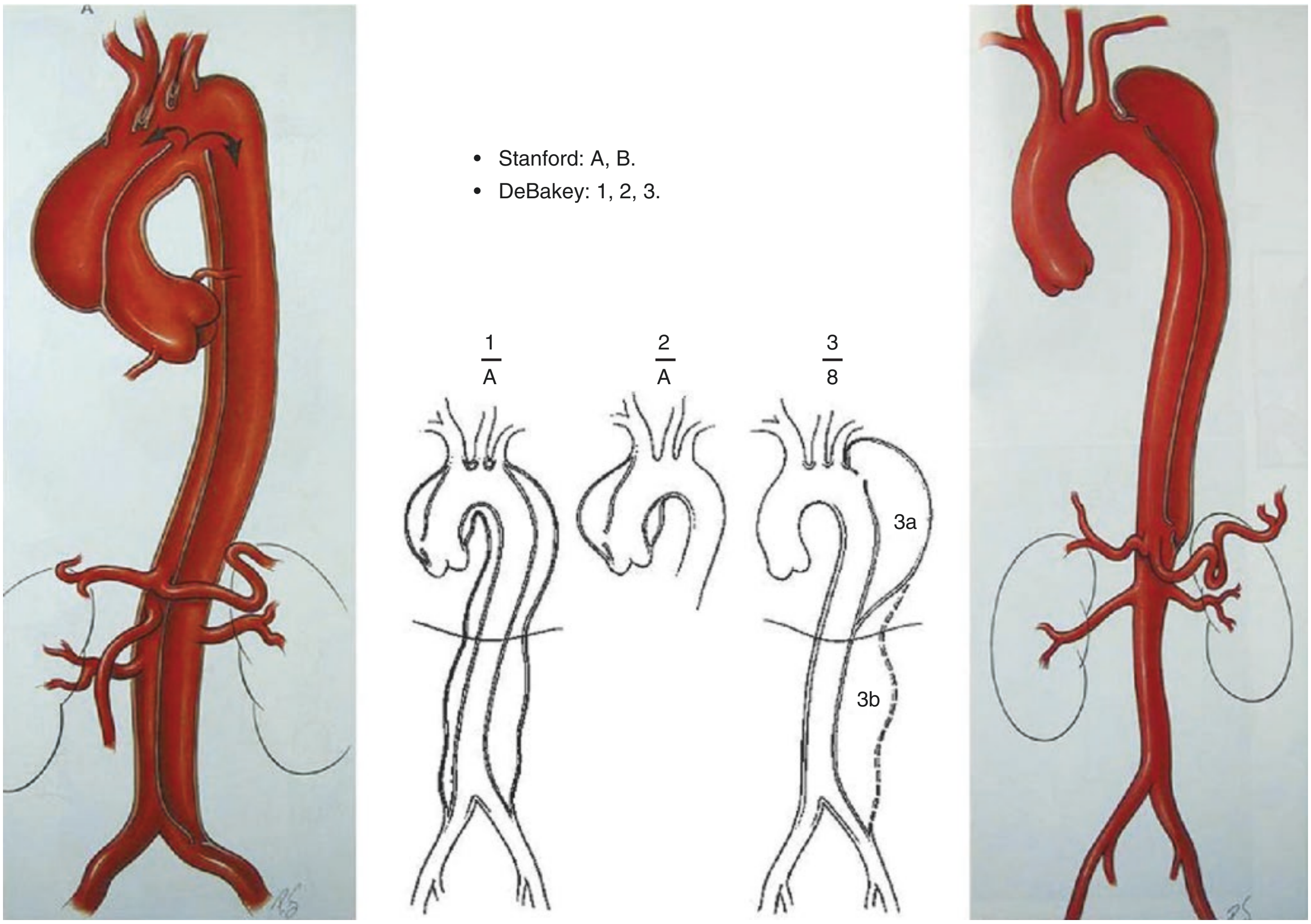

Fig. 53.2 DeBakey and Stanford classification systems for aortic dissection. DeBakey type I (Stanford type A): dissection involving the proximal aorta, arch and descending aorta; DeBakey type II (Stanford type A): dissection involving the ascending aorta alone; DeBakey type IIIa (Stanford type B): dissection involving the descending thoracic aorta alone beyond the left subclavian artery; DeBakey type IIIb (Stanford type B): dissection involving the descending thoracic and thoracoabdominal aorta. Of note, neither of current classification systems adequately describes the rarer subset of dissections limited primarily to the aortic arch. (Adapted from Refs. [1, 10])

Clinical Presentation and Diagnosis

Diagnosis of acute aortic dissection can be challenging as patients present with symptoms that can be seen with many other acute medical conditions. Acute type B aortic dissection (ATBAD) most commonly presents with sudden onset severe back pain, and according to the IRAD studies, 70% of patients with ATBAD present with concomitant hypertension. Hypotension in type B dissection is uncommon, presenting in less than 5% of patients. Thus, in patients with type B dissection and hypotension, aortic rupture must be ruled out [10]. Physical examination should include a neurologic assessment, musculoskeletal evaluation, and pulse checks. Spinal cord ischemia is seen in 2–3% of patients and 30–50% of patients present with pulse deficits [10]. Independent predictors of death with acute type B dissection, known as the “deadly triad”, include hypotension, absence of chest or back pain, and branch vessel (iliac, mesenteric, or renal) involvement [7, 11]. Additional risk factors for in-hospital mortality include prior aortic aneurysm, atherosclerosis, pleural effusion and female gender [12]. ATBAD requires prompt diagnosis and treatment. Thin-cut CT angiography of the chest, abdomen and pelvis is the diagnostic study of choice and should be performed without delay when suspicion for dissection exists. CT angiography allows for rapid assessment of dissection extent, location and size of primary tear, and evaluation of complicating features including rupture and malperfusion. Other imaging modalities which are diagnostic, though not as expeditious as CTA, include magnetic resonance angiography (MRA), aortography with or without intravascular ultrasound (IVUS), and transesophageal echocardiography (TEE).

Table 53.1 Risk factors for aortic dissection

Demographic
Male sex
Advanced age
Black race
Modifiable risk factors
Atherosclerosis
Hypertension
Cocaine use
Smoking
Congenital disorders
Bicuspid aortic valve syndrome
Coarctation of the aorta
Congenital aortic stenosis
Familial aortic aneurysm and dissection (FTAAD)
Ehlers-Danlos syndrome
Loeys-Dietz syndrome
Marfan syndrome
Turner's syndrome
"Other" genetically triggered aortic disease
Acquired and inflammatory conditions
Aortitis
Aortic aneurysm
Cushing's syndrome
Giant cell arteritis
Pheochromocytoma
Polycystic kidney disease
Pregnancy
Sheehan's syndrome (postpartum pituitary gland necrosis)
Systemic lupus erythematosus
Syphilis
Takayasu arteritis
Traumatic
Iatrogenic
Trauma

Adapted from Refs. [1, 8, 23]

Management

Management of type B dissection requires appropriate categorization of the disease as acute, subacute or chronic as well as prompt identification of complications or risk factors for complications. The ultimate goal is to treat or prevent complications and to improve survival. Depending on the acuity and complication status of the dissection, management options include medical therapy with anti-impulse therapy, open surgical repair, thoracic endovascular aortic repair (TEVAR), as well as peripheral open surgical and percutaneous revascularization procedures. Management strategies will be discussed in the setting of dissection subtype.

Uncomplicated Acute and Subacute Type B Dissection

Uncomplicated dissections compromise up to 85% of all acute type B dissections in most series, and the majority of these patients survive their initial hospitalization with medical management alone. First line treatment for uncomplicated TBAD is beta blockade, with a target systolic blood pressure of 100–120 mmHg and heart rate below 60–70 beats per minute. This treatment strategy, termed "anti-impulse therapy", aims to reduce the force of left ventricular contraction and to limit aortic wall stress. Other medications including calcium channel blockers, sodium nitroprusside, renin-angiotensin inhibitors may be used in conjunction with or as alternative therapy in patients who do not respond to or do not tolerate beta blockers [2]. Anti-impulse therapy remains the preferred treatment for these patients with an in-house mortality rate of <10% [3]. Although this strategy has been shown to be beneficial in the short-term, a number of studies have demonstrated that 25–50% of medically treated patients develop late aortic complications, most commonly aneurysmal degeneration of the false lumen. Given the progressive nature of this disease, many have speculated that early TEVAR may prevent adverse outcomes in patients with acute or subacute uncomplicated Type B dissection.

The INSTEAD trial (Investigation of Stent in patients with type B Aortic Dissection) was the first prospective randomized study of elective stent graft replacement compared with optimal medical therapy in patients with uncomplicated subacute Type B dissection. Although TEVAR enhanced false-lumen thrombosis and aortic remodeling in 90% of patients, it failed to improve survival rates or reduce adverse events in patients at 2 years [13]. The study also demonstrated a relatively high rate of aorta-related deaths resulting from procedural complications in the TEVAR group, including access vessel rupture, retrograde type A aortic dissection, and thoracic aortic rupture, albeit in the setting of an earlier generation TEVAR device. With the advent of improved devices, more recent studies have reported much lower periprocedural complication rates [3]. Further, follow-up at 5 years (INSTEAD-XL) demonstrated a significant benefit for aorta specific mortality in patients who underwent TEVAR (6.9% vs. 19.4%; $p = 0.04$) [14]. The ADSORB (Acute Dissection Stent grafting or Best medical treatment) trial, a prospective multicenter randomized trial in uncomplicated ATBAD, also demonstrated favorable aortic remodeling with false lumen thrombosis in patients treated with best medical therapy plus TEVAR when compared to best medical therapy alone [15]. Of note, there was no survival benefit demonstrated with TEVAR, and similar numbers of patients in both groups developed aneurysmal dilation of their aorta at 1 year [15]. This is consistent with other studies demonstrating that TEVAR used in treatment of TBAD does not prevent continued aneurysmal aortic degeneration [16].

Finally, since not all patients with type B dissection will require intervention in late follow up, some have suggested early TEVAR for "high risk" patients. For example, several recent studies have identified a number of risk factors for delayed complications in patients with otherwise uncomplicated TBAD. These include a false lumen diameter >2.2 cm, maximal transaortic diameter >4.4 cm, primary tear size >1 cm, rapid expansion (>1 cm/year), and partial false lumen thrombosis [17–19]. There is a critical need for a randomized controlled trial to further explore whether there may be a role for expanded indications for treatment of uncomplicated ATBAD with high risk features with TEVAR.

Complicated Acute Type B Aortic Dissection (ATBAD)

As discussed earlier, complicated ATBAD includes patients with rupture or clinical evidence of malperfusion due to compromised aortic branch flow; some would also include patients with refractory pain or hypertension despite optimal medical management in this complicated category. In patients with acute type B dissection with malperfusion or rupture, thoracic endovascular stent grafting has emerged as the standard of care (Class 1 indication, Level of evidence A), having largely replaced open surgery or fenestration in the current era [3, 18, 20].

It is important to recognize that malperfusion secondary to aortic branch vessel compromise may have different clinical presentations depending on the location, extent and type of malperfusion syndrome. Patients with compromised aortic branch flow may present with established end-organ ischemia, transient or intermittent symptoms of malperfusion, or "radiographic only" malperfusion with no clinical evidence of ischemia despite radiographic findings suggesting branch vessel compromise. High resolution thin cut CT angiography should be used to assess for compromised aortic branch flow and to distinguish *dynamic* from *static* aortic branch obstruction [10, 18] (Fig. 53.3). In dynamic malperfusion, the aortic branch true lumen is compressed by the pressurized false lumen. In this scenario, coverage of the primary

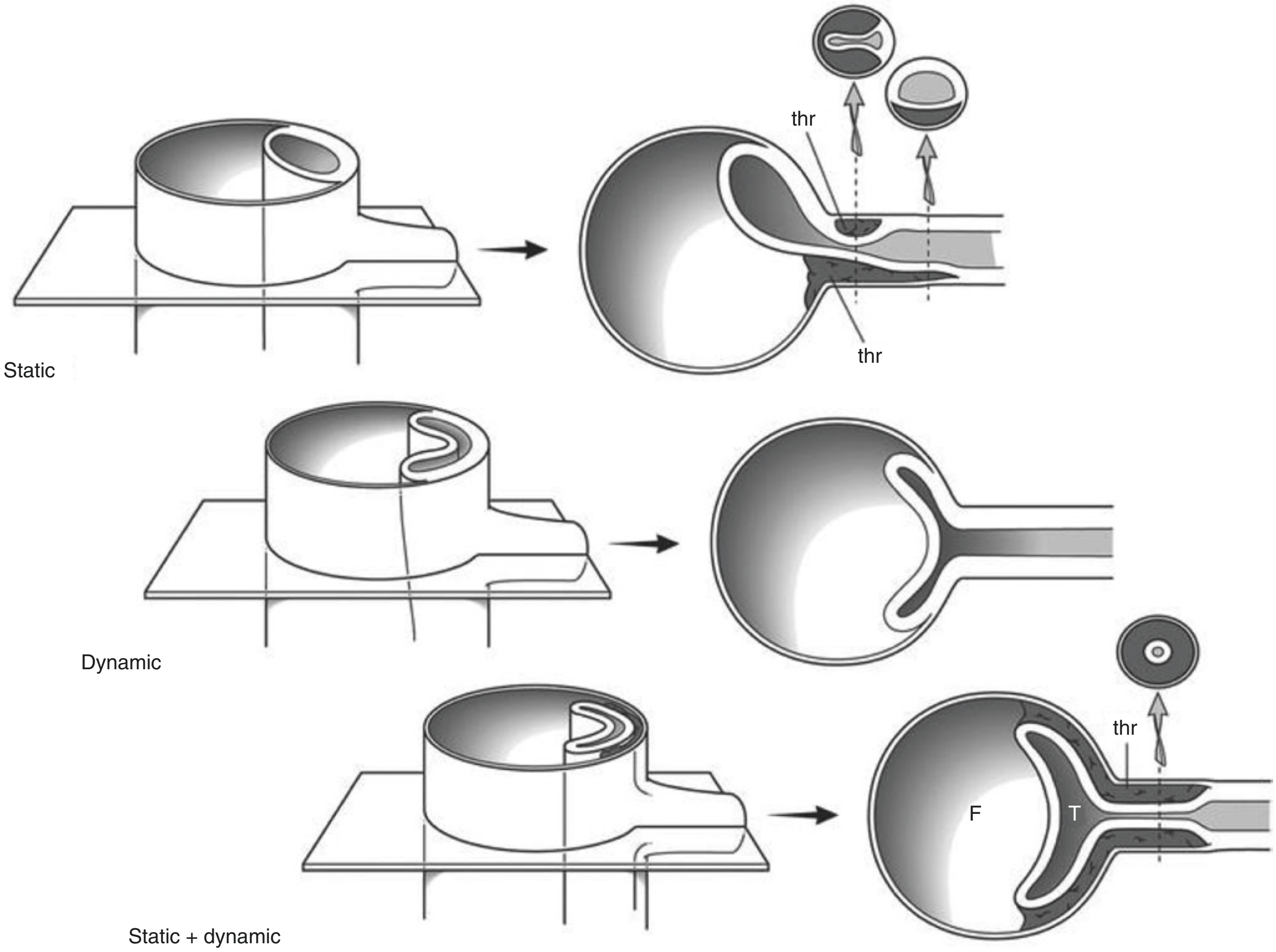

Fig. 53.3 Static malperfusion, where the dissection process extends into the aortic branch, typically with distal branch occlusion. In dynamic malperfusion, the aortic branch true lumen is compressed by the pressurized false lumen. Combined occlusions may occur as well. (Adapted from Refs. [41, 42])

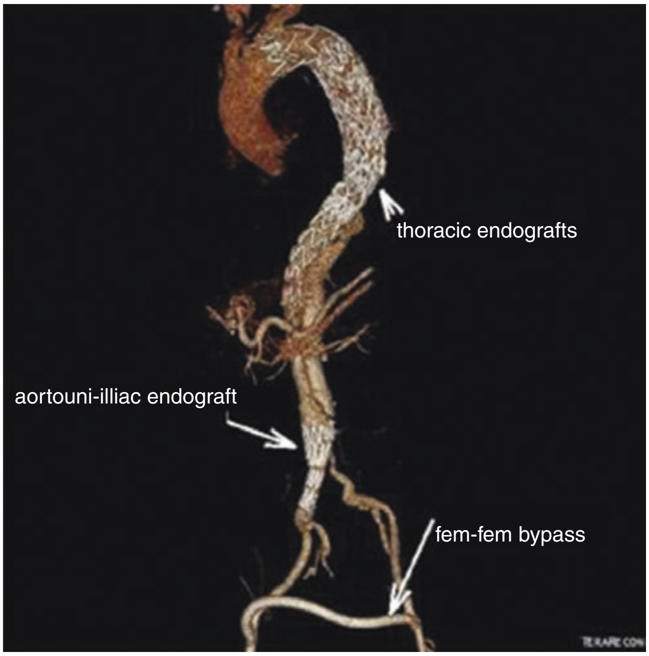

Fig. 53.4 Follow up CT angiography reconstruction demonstrating proximal thoracic endografting, aortouni-iliac endografting, and femoral-femoral bypass for management of a complicated TBAD with preoperative long segment left iliac occlusion. (Reproduced with permission from Ref. [21])

tear with a stent graft will most often relieve the dynamic obstruction by reducing flow to the false lumen, although in some cases additional procedures such as distal thoracoabdominal stenting or bypass may be required if there are large downstream fenestrations which continue to supply the false lumen. Static malperfusion, where the dissection process extends into the aortic branch, typically with distal branch occlusion, is a more difficult clinical problem to address. Management with TEVAR alone will fail to resolve static obstructions in at least 40% of cases, and often requires concomitant branch vessel stenting, septal fenestration, or selective branch vessel bypass to address malperfusion [18, 21] (Fig. 53.4) . This highlights the increased complexity in managing patients with TEVAR for aortic dissection when compared to isolated aortic aneurysms.

Chronic Type B Aortic Dissection (CTBAD)

In patients with uncomplicated TBAD, 20–40% will require late surgical intervention, most commonly due to false lumen dilation [22]. Long-term survival of patients with chronic type B dissection managed medically is poor, with a reported mortality of 50% at 5 years [18]. It is important to note that delayed mortality often is not related to aortic pathology, as 40–70% of these late deaths are a result of comorbid conditions, most commonly cardiac disease and stroke [2]. Expansion of the false lumen with the development of aortic aneurysm increases the risk of rupture, requiring close surveillance of patients after initial diagnosis. Intervention is indicated in suitable patients with chronic aortic dissection with an aortic diameter of ≥5.5 cm (Class 1, Level of evidence B) [23]. Traditionally, suitable patients have been treated with open surgery, usually via a left chest approach. Surgical resection may be extensive, frequently including the distal aortic arch and thoracoabdominal aorta beyond the diaphragm.

Although thoracic stent grafts are approved for chronic type B dissection, no clinical trials have been performed to demonstrate a reduced risk of aortic rupture. Given the lower procedural morbidity and mortality, TEVAR has been increasingly performed for the treatment of chronic type B dissection with associated thoracic aneurysmal degeneration. Early critics of TEVAR for chronic type B dissection raised concerns that the distal abdominal fenestrations, which remained uncovered, would continue to back-fill and pressurize the false lumen and that the chronically thickened dissection flap would fail to reverse remodel after treatment. Despite these concerns, several studies have demonstrated that the majority of CTBAD treated with TEVAR had successful false lumen depressurization and thrombosis with reverse remodeling and decreased aneurysm size [22]. Further, a European expert consensus document recommends TEVAR for management of CTBAD with appropriate anatomy, citing reduced early mortality when compared with open surgery. They recommend that open surgery should be reserved for cases where anatomy is inappropriate or for patients with connective tissue disorders [24].

Penetrating Aortic Ulcer and Intramural Hematoma

It is important to distinguish acute aortic dissection from penetrating aortic ulcer (PAU) and intramural hematoma (IMH) within the spectrum of acute aortic syndromes (Fig. 53.5). Although PAU and IMH often have similar clinical presentation to aortic dissections and overlapping risk factors, they have a distinct pathogenesis and diagnostic findings. PAU is most often associated with significant atherosclerotic disease and occurs when an atherosclerotic plaque disrupts the inner layers of the aorta. PAU may also occur in the setting of prior TEVAR at the distal or proximal junction of the aorta and endograft [25]. PAU may be found in isolation or in association with IMH. PAU in isolation are often asymptomatic and found incidentally on imaging for other indications; they may develop aneurysmal dilation with risk of rupture and therefore large (>2 cm saccular depth) asymptomatic PAU should be treated. When a PAU invades the media, a localized hemorrhage into the wall occurs (IMH) without a dissection flap.

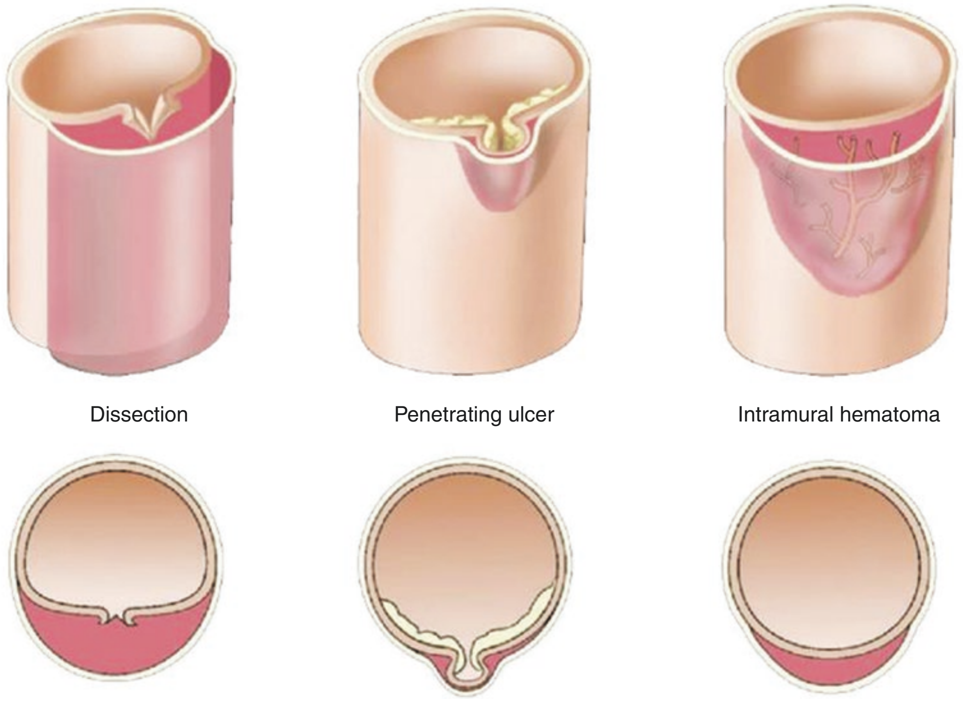

Fig. 53.5 Illustration demonstrating differences between aortic dissection, penetrating ulcer, and intramural hematoma. In aortic dissection there is a propagating separation between the true and false lumens. Penetrating ulcers are often associated with significant atherosclerotic disease and occur when an atherosclerotic plaque disrupts the inner layers of the aorta. Intramural hematoma is a localized hematoma in the aortic wall without a clear intimal tear. (Adapted from Ref. [43])

An IMH represents a localized hematoma in the aortic wall without a clear intimal tear, although an associated PAU is nearly always present. Classically, IMH was believed to develop from a ruptured vasa vasorum in the aortic wall; however, this hypothesis is controversial and lacks pathologic confirmation. Recent studies in the setting of improved imaging demonstrate that there are small intimal lesions (PAU) without a dissection flap [26, 27]. Further larger scale studies are needed to better define this pathologic process. IMH most often occurs spontaneously in hypertensive patients but may also develop in the setting of a PAU or thoracic trauma [18, 28]. It most commonly occurs in the descending aorta, and is more frequently seen in older males [27, 29–31].

Follow-Up

Surveillance imaging is critical to the care of patients after aortic dissection. As mentioned, even with optimal medical management, at least one third of patients will develop aortic complications within 5 years of their dissection requiring surgical treatment. Unfortunately, many patients may be lost to follow-up [7, 32]. Lower socioeconomic status has been linked to reduced early and late survival after dissection [33–35]. This may be in part due to decreased compliance with medication and surveillance protocols. Thus, close clinical follow-up and advocacy to reduce insurance-based disparities is paramount to the care of these patients. As mentioned earlier, delayed mortality in aortic dissection patients often results from comorbid diseases, most commonly from cardiovascular disease. In addition to strict blood pressure control, lipid profile should be optimized, antiplatelet therapy initiated as necessary, and patients should be encouraged regarding regular exercise, weight reduction and smoking cessation. Antihypertensives should be administered as needed with a target blood pressure of less than 140/90 mmHg for patients without diabetes, and less than 130/80 mmHg for patients with diabetes or chronic kidney disease (Class 1, Level of evidence B) [23]. In patients with Marfan syndrome, an angiotensin receptor blocker to reduce the rate of aortic dilation is reasonable (Class 2a, Level of evidence B) [23]. Statin use to achieve a target LDL below 70 mg/dL in patients with coronary artery disease (CAD) or CAD risk should also be considered (Class 2a, Level of evidence A) [23]. After initial aortic dissection, PAU or IMH, routine surveillance imaging is recommended. Though no robust evidence is available to guide surveillance, the AHA consensus document suggests imaging at 1, 3, 6 and 12 months. If stable at 1 year, imaging can be performed annually (Class 2a, Level of evidence C) [23]. Follow-up thin slice CT angiography scans must include both arterial phase and delayed contrast imaging to fully detect late false lumen perfusion (Fig. 53.6). Other imaging techniques including MRA and echocardiography may be considered in select patients. Ultimately, long-term surveillance modality and timing should be individualized to patient characteristics to minimize unnecessary exposure to radiation [36].

These recommendations allow for early recognition and repair of delayed complications of TBAD, the most common of which is aneurysmal dilation of the false lumen. Similarly,

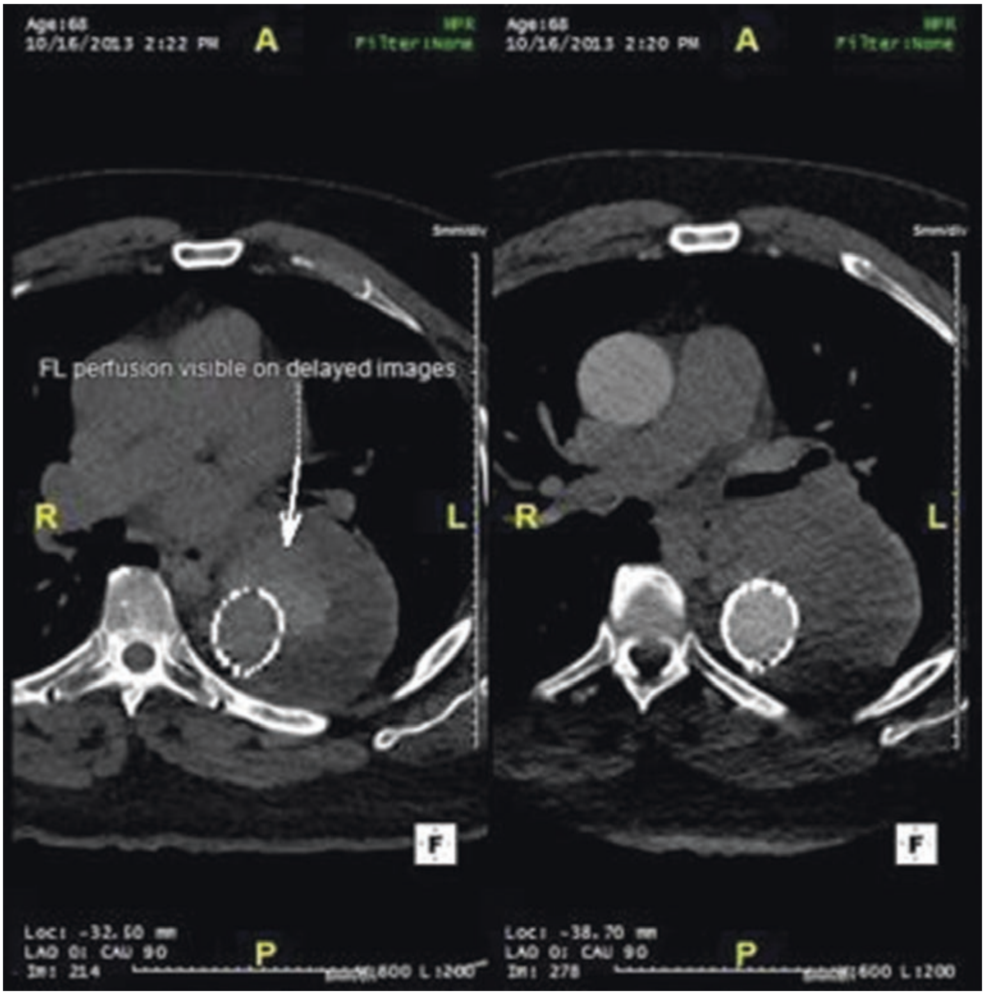

Fig. 53.6 Arterial phase (right) and delayed phase (left) imaging in a patient status post TEVAR for chronic aortic dissection. Note that false lumen appears thrombosed in arterial phase image on right, whereas the delayed phase image clearly demonstrates continued perfusion of the false lumen

serial imaging and follow-up should be performed in patients who have had TEVAR. In addition to maintaining optimal medical management after TEVAR, the surgeon should document evidence of favorable aortic remodeling (true lumen expansion and false lumen shrinkage with stable or decreasing overall aortic diameter) and be vigilant in surveilling for endoleaks, stent-graft induced new entry tears (SINE), penetrating aortic ulcers at the proximal or distal endograft landing zones, retrograde type A dissection, and other aorto-vascular disease at sites remote from the TEVAR [25]. Notably, a systematic review of medium- and long-term outcomes after TEVAR for TBAD has not demonstrated prevention of aneurysmal dilation of the aorta [16]. In addition, recent studies have indicated that unfavorable cardiac remodeling may develop late after TEVAR, perhaps due to graft non-compliance resulting in increased LV stroke work [37, 38]. These findings may necessitate further cardiac functional surveillance. Family or personal patient history of prior aortic dissection, aortic aneurysm, bicuspid aortic valve disease and connective tissue disorders or sudden unexplained deaths in relatives should prompt investigation into connective tissue disorders with genetic testing, family screening and counseling as needed. As such, a multidisciplinary approach should be employed as necessary and many centers have adopted an "Aortic Team" model [39, 40].

Conclusions and Future

TEVAR is standard of care for complicated ATBAD with either rupture or malperfusion. For initially uncomplicated cases, optimal medical management with anti-impulse therapy currently remains the first-line treatment, although many studies have suggested a more aggressive approach to these patients and a randomized controlled trial is clearly needed to answer this question with more certainty. TEVAR may also be effective in the treatment of select patients with CTBAD. There have been many recent advances in device technology with clinical trials currently underway. These devices may allow for more complex endovascular repair of aortic dissections utilizing branch graft devices and more conformable technology. The management of patients with type B dissection will continue to evolve and remains an area of intense investigation among those with an interest in aortic disease.

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Check for updates

Chronic Type B Aortic Dissection

54

Konstantinos Spanos and Tilo Kölbel

High Yield Facts

- Type B dissection was initially classified as chronic if the patient survived beyond a two-week time-period and lately > 90 days.
- Imaging of the complete aorta is recommended to evaluate a patient with chronic type B aortic dissection (CTBAD).
- CT angiography is the most commonly used modality to assess aortic dissection since it is widely available, accurate, operator independent, fast and offers a high resolution.
- European Society for Vascular Surgeons (ESVS) guidelines recommend that in patients with chronic aortic dissection effective antihypertensive therapy and beta blockers must be administered.
- Current indications for operative treatment of CTBAD include rupture or bleeding, false lumen aneurysm of >5.5–6 cm, false lumen growth ≥5 mm/year and malperfusion.
- DISSECT, a mnemonic classification is proposed to influence therapeutic decisions in current practice.
- Thoracic endovascular aortic repair (TEVAR) has become the preferred treatment option for type B dissections compared to open surgical repair (OSR).
- OSR of CTBAD is limited to highly specialised vascular centers with profound experience in open thoraco-abdominal aortic repair.

Introduction

Diseases of the aorta have increasingly been the center of clinical focus during the last decade, mainly due to their dismal prognosis and the development of new minimal invasive treatment techniques [1]. One of the major pathologic aortic entities is aortic dissection (AD). Aortic dissection (AD) was first reported in 1761 in the necropsy of King George II [2]. Since then, the incidence of AD which has been previously estimated at 3.5/100,000 patient-years [3], appears to have increased to 14/100,000 [4]. Thus, aortic dissection accounts for 43,000–47,000 deaths in the United States each year [5]. Thoracic ADs not involving the ascending aorta and arch are defined as Stanford B (DeBakey IIIa, IIIb) (Fig. 54.1) [1]. The timing of presentation related to symptom onset is another critical prognostic and classification factor. The classification as "chronic" was set for patients with type B dissection initially beyond a two-week time-period [1]. That was mainly supported by the International Registry of Acute Aortic Dissection (IRAD) [6] which has followed over 5000 patients in 11 countries, and showed that among untreated patients, the majority (75%) of mortalities occur within 2 weeks of symptom onset, whereas the 30-day survival of patients surviving the first 2 weeks is 90% [7]. However, IRAD study has also suggested four distinct chronological subgroups: hyper-acute (up to 24 h); acute (2–7 days); subacute (8–30 days); chronic (>30 days) [8]. Additionally, Steuer et al. [9] have suggested as a chronic phase the limit of >90 days based on the fact that a significant number of acute complications, particularly rapid enlargement and distal ischemia, appear up to 90 days after initiation.

Imaging

Imaging of the complete aorta is recommended to evaluate a patient with CTBAD. CT angiography (CTA) (Fig. 54.2a), magnetic resonance imaging (MRI) (Fig. 54.2b), and

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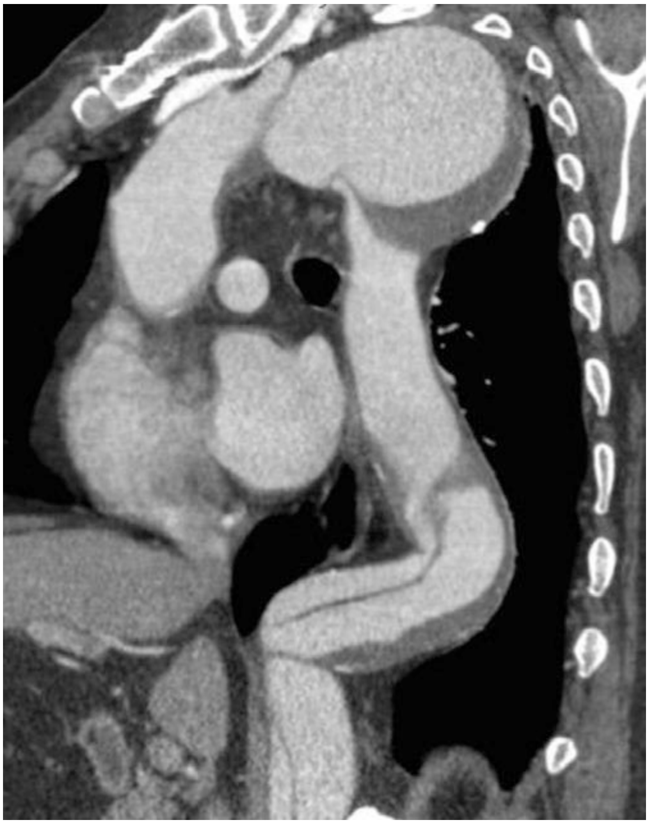

Fig. 54.1 Multiplanar reconstruction of CT-angiography of chronic type B aortic dissection and false-lumen aneurysm in the proximal descending thoracic aorta

trans-esophageal echocardiography are all reliable imaging modalities [10]. Transesophageal echocardiography offers accurate examination with a sensitivity of 80% with better assessment of entry tears and true lumen compression [11]. However, CTA is the most commonly used modality to assess aortic dissection since it is widely available, accurate, operator independent, fast and offers a high resolution. The use of ECG-gated CTA imaging is currently recommended to overcome pulsation artifacts in cases with ascending aorta involvement [12]. Contrast-enhanced MRI with its delayed phase acquisitions with use of blood pool agents may improve visualization of the false lumen status, which may be overestimated with first pass CTA imaging [13]. Moreover, time resolved MR angiography provides an assessment of flow dynamics. This can reveal new potential dynamic predictors of complications in TBAD patients, such as vessel malperfusion, helical blood flow in the false lumen, velocity, and false lumen stroke volume [14].

Best Medical Treatment

In the very recent European Society for Vascular Surgeons (ESVS) guidelines [15] it is recommended that in patients with chronic aortic dissection effective antihypertensive therapy and β-blockers must be administered (Table 54.1).

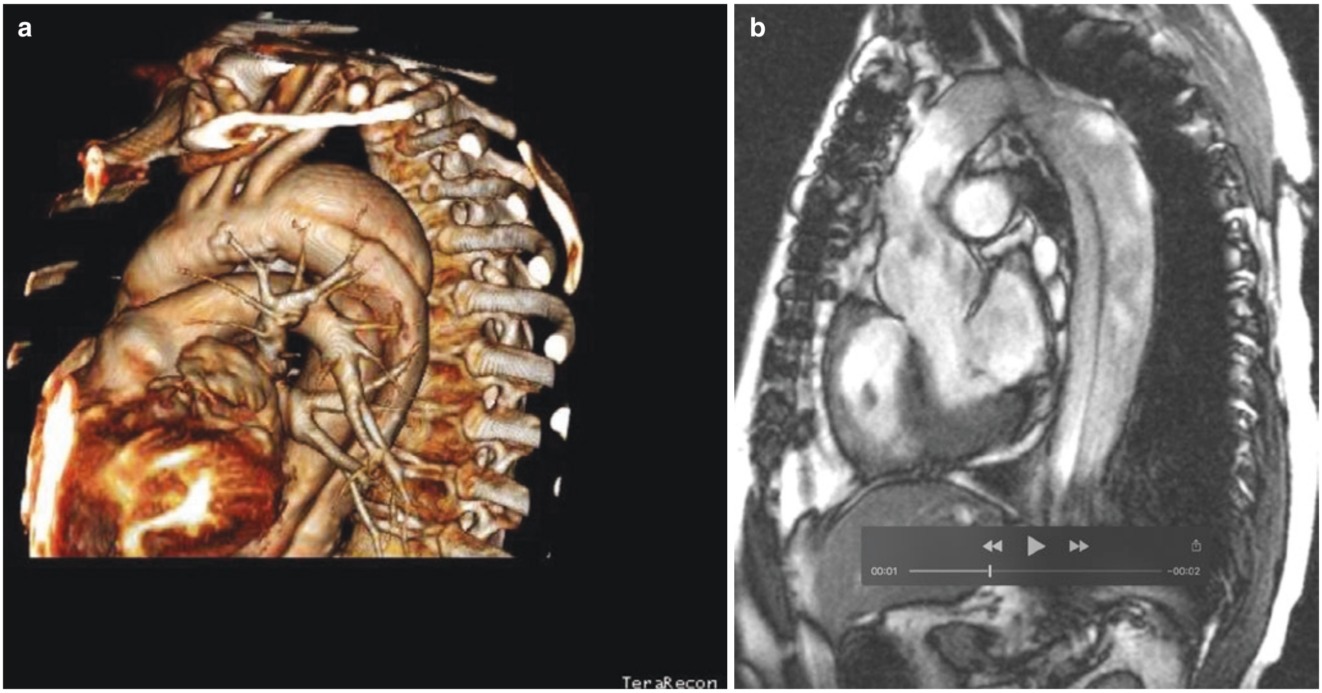

Fig. 54.2 (**a**) 3D volume rendering of a CT angiography with chronic type B aortic dissection. (**b**) Magnetic resonance angiography with chronic type B dissection

Table 54.1 ESVS guidelines on medical treatment of CTBAD[a]

Recommendation	Class	Level of evidence
Effective antihypertensive therapy should be given to reduce the risk of aortic related death	I	C
Measures to reduce cardiovascular risk such as treatment of hyperlipidaemia, anti-platelet therapy, and smoking cessation should be implemented	I	C
Long-term medical treatment with β-blockers should be given to patients as they reduce the progression of aortic dilatation, the incidence of subsequent hospital admission, and the need for late dissection related aortic procedures	I	C

[a]From Ref. [15]

Indications for Intervention

Current indications for operative treatment of CTBAD include [16]:

- Rupture or bleeding
- False lumen aneurysm of >5.5–6 cm
- False lumen growth 5 mm/year and more
- Malperfusion

Most recently DISSECT [17], a mnemonic classification, has been proposed to influence therapeutic decisions in current practice (Table 54.2).

Table 54.2 The DISSECT classification of aortic dissection[a]

Duration of disease
Intimal tear location
Size of the dissected aorta
Segmental extent of aortic involvement
Clinical complications of the dissection
Thrombus is absent/present within the false lumen

[a]From Ref. [17]

Invasive Treatment

Since 1999, when Nienaber et al. [18] published their report on the nonsurgical insertion of an endovascular stent-graft in selected patients who had thoracic aortic dissection, thoracic endovascular aortic repair (TEVAR) has become the preferred treatment option for type B dissections compared to open surgical repair (OSR).

Open Surgical Repair

Nowadays, OSR of CTBAD is limited to highly specialised vascular centers with extensive experience of open thoracoabdominal aortic repair. The majority of OSRs involve graft replacement of the diseased aorta, while in some cases only closure of the entry tear and plication of the aneurysm may take place [19]. A wide range of spinal cord protection strategies can be used such as cerebrospinal fluid (CSF) drainage, selective intercostal artery reimplantation, motor evoked potentials (MEP) and hypothermic circulatory arrest. In a recent systematic review of the literature regarding OSR for CTBAD [19], 19 studies were included with 970 patients undergoing OSR for CTBAD at a mean age of 58 years. Early mortality at 30 days was 11.1% (range, 0–33%), while early morbidity included stroke 5.6% of patients (range, 0–13%), spinal cord ischemia (SCI) 4.9% (range, 0–13%), postoperative renal dysfunction in 11.9% (range, 0–33%) and subsequent re-exploration for bleeding was required for 9.9% of patients (range, 0–33%). However, the analysis of this data using Kaplan-Meier methods demonstrated 1-, 2-, 3-, 5-, and 10-year survival of 82.1%, 77.1%, 74.1%, 66.3%, 50.8%, respectively.

Endovascular Repair

Thoracic endovascular aortic repair (TEVAR): Current devices used for the endovascular treatment of CTBAD include the Zenith Dissection Endovascular System and TX-2 ProForm (Cook Inc., Bloomington, IN), TAG (W.L. Gore and Associates), Talent and Valiant (Medtronic Inc., Santa Rosa, CA), and Relay (Bolton Medical, Inc., Sunrise, FL). The Zenith Dissection Endovascular System is a modular, two-piece design with the proximal segment being a barbless Zenith TX2 thoracic aortic endovascular graft with Pro-Form, and a distal bare metal dissection stent which consists of multiple self-expanding Gianturco stainless steel Z-stent segments that are sewn end-to-end with braided polyester suture. This design may allow the treatment of a longer segment of the dissection flap of the native aortic wall without compromising the origins of the important branch arteries and decreasing the complication rate of SCI and organ malperfusion. This stent-graft system was based on Nienaber, who first described the provisional extension to induce complete attachment after stent-graft placement in type B AD (PETTICOAT technique) involving extension of the coverage zone by a bare stent to obliterate persistent false lumen [20]. The Gore TAG Endoprosthesis, consists of an expanded PTFE (ePTFE) and fluorinated ethylene propylene (FEP) tube attached to an exoskeleton of nitinol stents with ePTFE-FEP bonding tape. The Medtronic Talent Thoracic Stent Graft System consists of a self-expanding, nitinol endoskeleton attached to a woven polyester graft. Further development of the Talent design has resulted in the Valiant thoracic stent-graft design in which the longitudinal connecting bar has been removed and a modified proximal FreeFlo design with a proximal bare-stent was added. The Relay Thoracic Stent-Graft consists of self-expanding nitinol stents sutured to a polyester graft fabric. This stent-graft is available with and without a proximal bare-stent.

The pre-operative planning of endovascular treatment of CTBAD with either of these stent grafts systems includes four major considerations (Table 54.3).

Evidence regarding the efficacy and long term results of TEVAR for CTBAD derives from two recent randomized trials: The Investigation of Stent Grafts in Aortic Dissection with extended length of follow-up (INSTEAD-XL; extended for late follow-up) [21] and the The INvestigation of STEnt grafts in Aortic Dissection (INSTEAD) trial [22]. In the first one, a total of 140 patients with stable TBAD previously randomized to optimal medical treatment and TEVAR (n = 72) versus optimal medical treatment alone (n = 68) were analyzed retrospectively for aorta specific, all-cause outcomes, and disease progression using landmark statistical analysis of years 2–5 after index procedure. The risk of all-cause mortality (11.1% versus 19.3%; P = 0.13), aorta-specific mortality (6.9% versus 19.3%; P = 0.04), and progression (27.0% versus 46.1%; P = 0.04) after 5 years was lower in endovascular group than with optimal medical treatment alone. On the other hand, in INSTEAD trial, which included 140 patients in stable clinical condition at least 2 weeks after index dissection (elective stent-graft placement in addition to optimal medical therapy in 72 versus optimal medical therapy alone in 68), endovascular repair did not improve 2-year survival and adverse event rates; however TEVAR allowed a favorable aortic remodeling.

Table 54.3 Preoperative considerations for TEVAR

Proximal fixation zone	Proximal sealing zone of at least 15–20 mm to the primary entry tear and sealing in non-dissected aortic wall
Device sizing	Oversizing usually 10–20% to ensure firm anchoring and a tight circumferential seal. This oversizing meets instructions for use of Zenith Dissection System and Relay grafts. Valiant stent-grafts are recommended to be oversized up to 10% and Gore TAG between 8% and 32%
Distal fixation zone (after device sizing)	No oversizing is recommended related to the crescent length of the frequently compressed true lumen in order to avoid stent-graft induced new entry tears (SINE)
Windsock effect	This can be overcome by reducing the cardiac output with pharmacological agents, right ventricular pacing, and cardiac preload reduction by inferior vena cava balloon occlusion

Fenestrated and/or branched stent-grafts: Recently, new stent-grafts have been developed for the aortic arch with either fenestrations or branches, in order to encompass the supra-aortic vessels for cases where a more proximal sufficient sealing zone is needed for the endovascular treatment of AD, thus for CTBAD too [23]. The inner branched device by Cook Medical is a custom-made device designed according to each patient's anatomy with two inner side branches for the innominate trunk (IT) and the left common carotid (LCC) that can be used in such cases [24]. Additionally, fenestrated custom-made device manufactured by Cook Medical (Fig. 54.3) constructed with either a single fenestration and a scallop or a single fenestration or a single scallop is another option for such cases [25]. The Bolton arch branch device which is based on the Relay NBS platform, is constructed similar to the Cook device, with two inner branches [26].

Recently, Oikonomou et al. [27] demonstrated that fenestrated and branched devices are a feasible option for patients with a post-dissection thoracoabdominal aneurysm (Fig. 54.4). Although associated with additional technical challenges, and a significant need for re-intervention, it leads to favorable aneurysm morphologic changes, and may play a more prominent role in the future for this type of pathology if long-term results substantiate the good initial outcome. Similar good results were also published by Kitagawa et al. [28].

False lumen occlusion techniques: In CTBAD, TEVAR alone was shown to be beneficial, but with a high rate of failure because of the continuing false lumen enlargement and subsequently higher rate of re-intervention and mortality [29]. This failure to remodel seems to be caused by retrograde perfusion to side branches arising from the false lumen [30]. Thus, after standard TEVAR complete false lumen thrombosis is only achieved in around 40% of the patients by

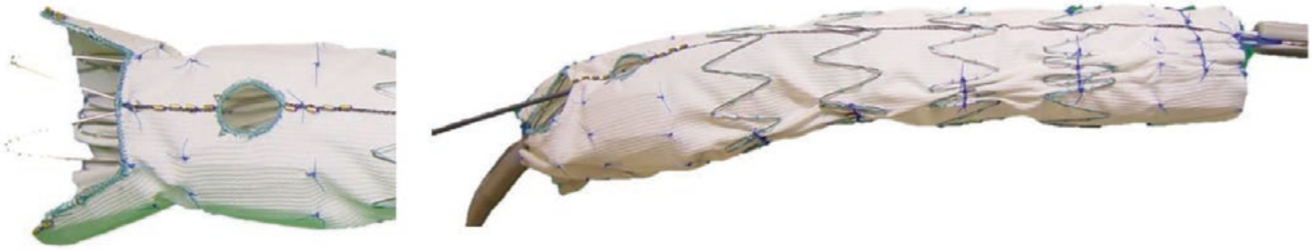

Fig. 54.3 The fenestrated custom-made device manufactured by Cook Medical

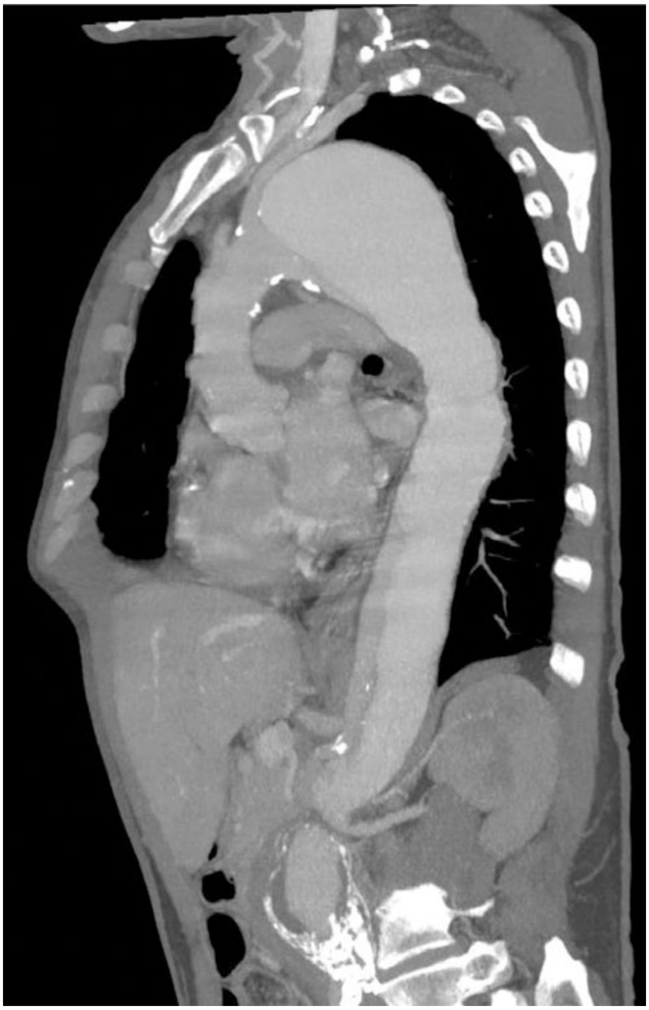

Fig. 54.4 Maximum intensity projection of CT angiography of patient with type B aortic dissection and a false lumen aneurysm of the thoracoabdominal aorta

covering the proximal tear entry alone [31]. The failure of false lumen thrombosis may lead to late false lumen expansion during follow up in 30% of patients treated with TEVAR requiring additional re-interventions [22, 32]. False lumen patency has been shown to be an independently associated predictor of poor long-term survival in CTBAD [33], while thrombosis of the false lumen may be an independent predictor of no further growth [34].

The first description of an endovascular approach to occlude the false lumen in order to prevent further enlargement is from 2003 by Loubert et al. [35]. Loubert and associates describe the use of different materials, such as IVC-filters, detachable balloons, thrombin and iliac occluders in two cases. Other materials and techniques that can be used for the false lumen occlusion after TEVAR are described below.

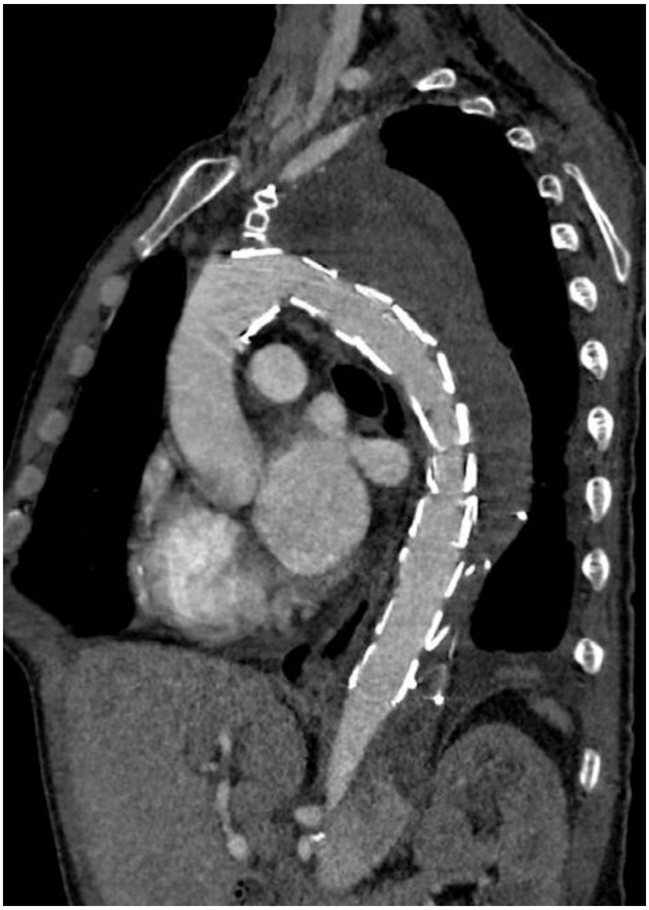

Fig. 54.5 Post-intervention CT after thoracic endovascular repair and candy-plug occlusion of the false lumen in the distal descending thoracic aorta. The left subclavian artery is covered and occluded with an Amplatzer vascular plug

The Candy-Plug technique: Kölbel et al. [36] described the Candy-plug technique in 2013 using a back-table modification of a Zenith thoracic TX2 Pro-Form stent-graft by adding a diameter-reducing suture and then using a 20-mm Amplatzer Vascular Plug II (AVP; St. Jude Medical, St. Paul, MN, USA) in the waist of the candy-wrapper shaped plug. The Candy-Plug is placed into the false lumen (maximum 36-mm diameter) down to the distal end of the true lumen stent-graft, occluding the false lumen proximal to the celiac artery to preserve flow to reno-visceral arteries while preventing false lumen backflow to the thoracic segment (Figs. 54.5 and 54.6). Recently, Rohlffs et al. [37] presented the results of Candy plug technique in 18 consecutive patients with thoracic false lumen aneurysm in chronic aortic dissection. It was shown that the Candy-Plug technique is a feasible endovascular method to achieve false lumen occlusion and aortic remodeling in chronic aortic dissection and it is associated with low morbidity and mortality.

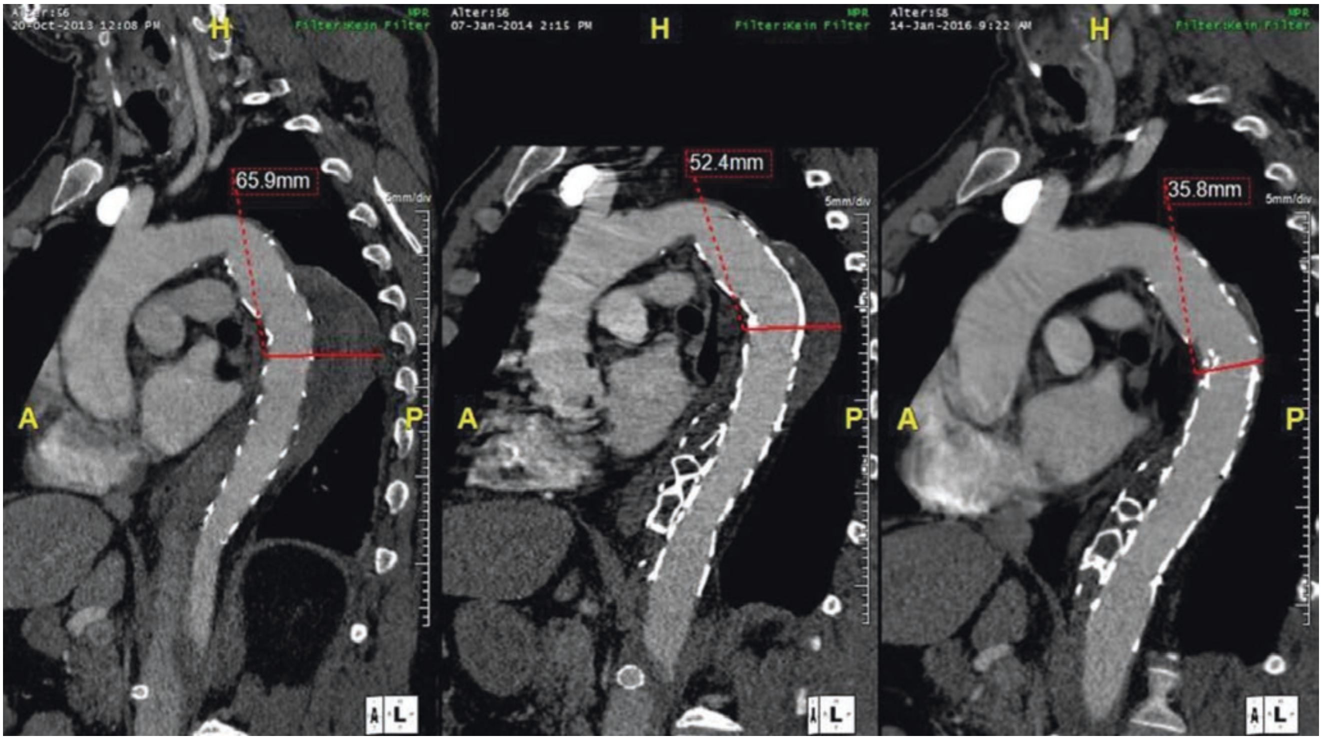

Fig. 54.6 Candy-plug technique

The Knickerbocker technique: The concept is based on the dilation of the middle part of a large diameter stent-graft that is placed in the true lumen [38] (Fig. 54.7). A short segment of the stent-graft is forcefully dilated using a compliant balloon to rupture the dissection membrane and extending the stent-graft to the false lumen. Instead of an oversized standard tubular stent-graft, a double-tapered graft construction with a bulbous section can be used. The main advantage of this technique is that it does not mandate the access of the false lumen, or the addition of more materials.

Vascular and iliac plugs- coils and glue embolization technique: A large variety of devices and solid as well as liquid embolization materials have been developed to occlude the false lumen [39–42] (Fig. 54.8). However, a major limitation is the diameter of the false lumen as most of these materials are commercially available up to 24 mm, requiring as a result using more than one device or a lot of adjunctive embolization material.

Considerations

False Lumen Deployment

One limitation in TEVAR for CTBAD frequently is the limited diameter of the true lumen. While our experience is that the true lumen expands after TEVAR or can be dilated during TEVAR to a reasonable diameter, in some cases the true lumen may be too small to place a standard TEVAR device or it may be completely occluded. In that situation placement of the TEVAR device partially in the false lumen can be a solution as long as the proximal and distal end of the stent graft or its branches seal in true lumen. Fenestration techniques are helpful in order to allow for the desired course of the reconstruction [43].

Stent Graft Induced New Entry (SINE)

During the endovascular treatment of CTBAD, the stent graft has the potential to cause intimal injury to the aorta and may result in new aortic dissection or pseudoaneurysm formation at distal end of the stent graft. Stent graft induced new entry (SINE), which is defined as a new intimal tear caused by the stent graft, is a major complication related to TEVAR in aortic dissection [44, 45] (Fig. 54.9). Complicated distal SINE can successfully be managed by distal endograft implantation. Increased oversizing of the distal stent graft may be a significant factor causing delayed distal SINE. Precise measurements and size selection is crucial for the distal end of the stent, especially for high taper ratio dissection pathology [44, 45].

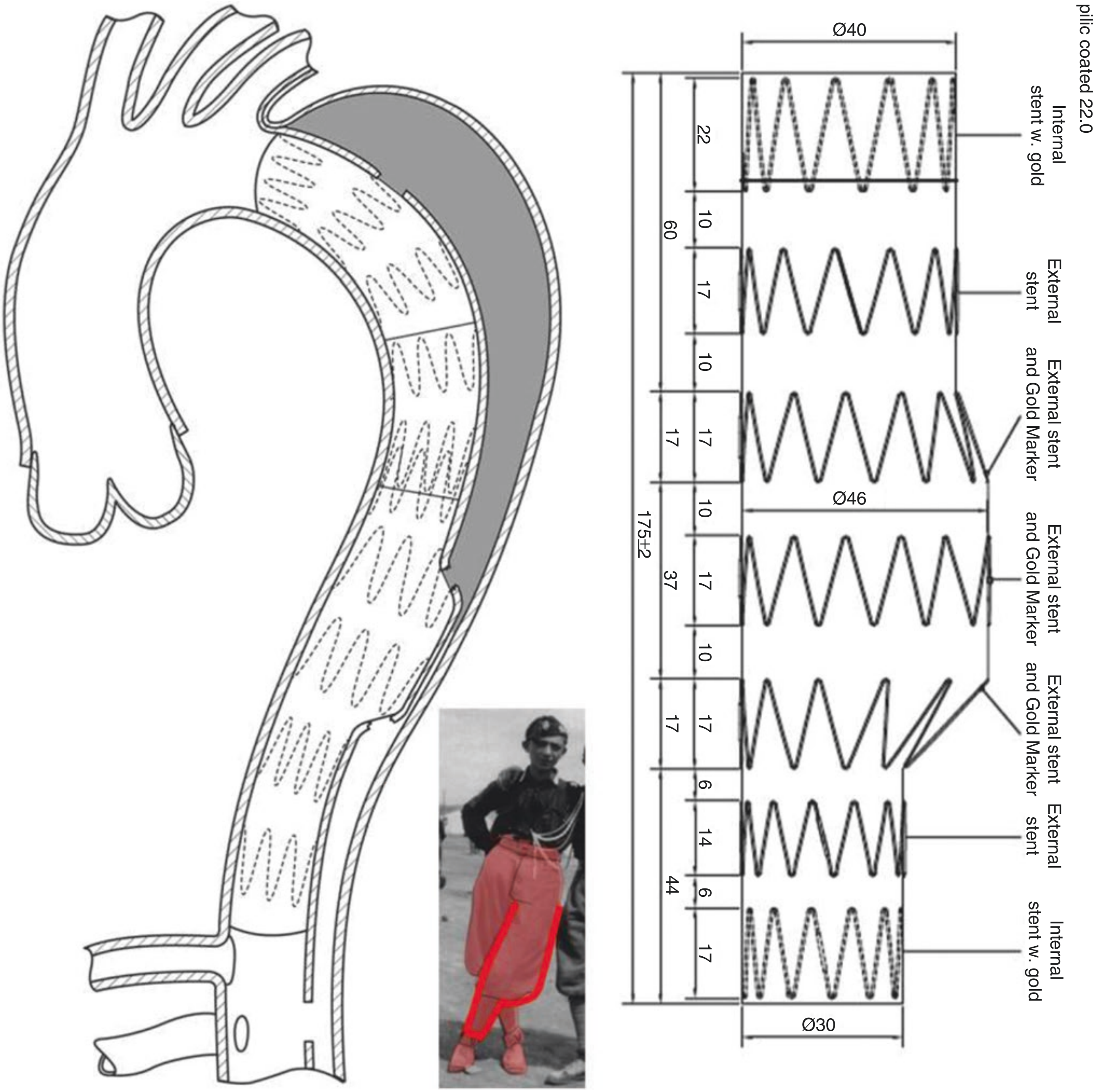
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Fig. 54.7 Knickerbocker technique

Adherence to Medical Therapy

Aggressive anti-impulse therapy is the cornerstone of management in the majority of patients with CTBAD who are currently managed conservatively. Guidelines recommend goal-directed therapy to achieve a heart rate of <60 beats per minute and systolic pressure of 100–120 mmHg, goals that may require a number of pharmacologic agents [15, 46]. However, the issue of adherence to medical treatment remains a major concern, as this factor may influence the clinical outcome of both conservatively managed patients as well as those that have undergone invasive procedure. Recently, it has been demonstrated in a cohort of patients with CTBAD, that only 43% of them reported high levels of medication adherence, while the rest of them reported either moderate or low adherence [47]. To develop an evidence-based treatment strategy for TBAD, one should take into account the direct and indirect effects of medical therapy and patients' adherence.

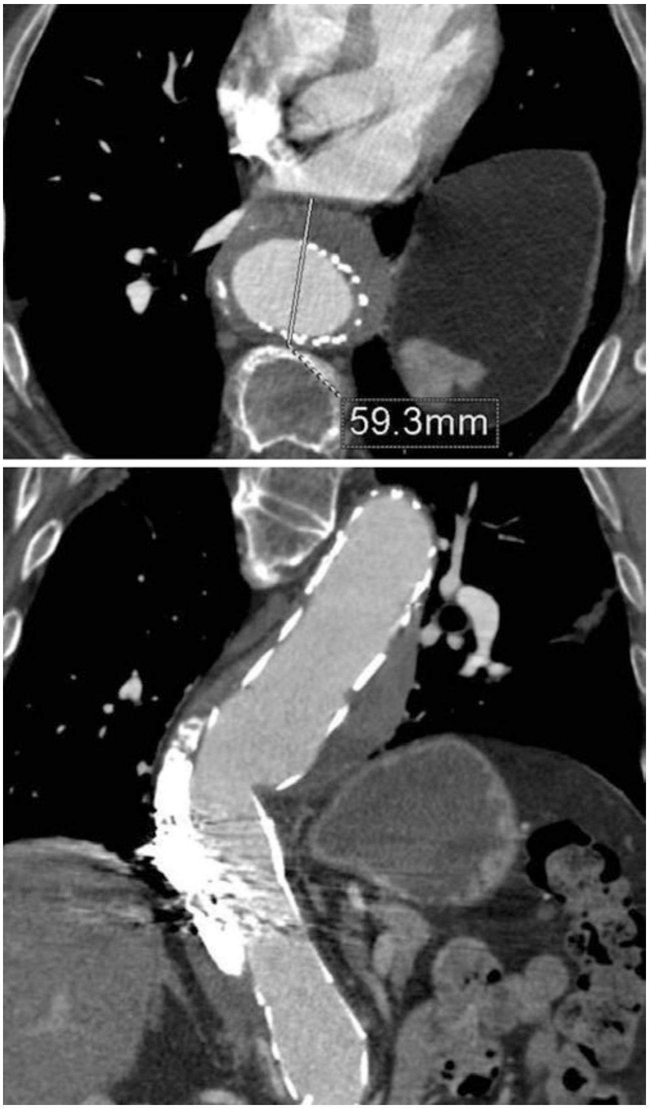

Fig. 54.8 False lumen thrombosis with coils

Level of Exercise

The recommendation of exercise in patients after CTBAD and generally after aortic dissection still remains a controversial issue. Evidence on the subject shows that exercise is probably doing more good than harm for patients with CTBAD, and therefore physicians should advise in favor of physical exercise [48]. Patients are interested in knowing the safe level of physical exercise and weightlifting as well as presence of other restrictions. This information should also include topics such as sexual activity or straining during defecation, as many patients are discouraged from discussing these issues. As there is lack of evidence for a negative overall effect of physical and sexual activity in post-dissection patients, the physician should focus the discussion with the patient on the proven benefit that physical activity has on long-term blood pressure management in order to overcome the persistent fear that physical activity may lead to the deterioration of their condition. There is no specific recommendation in the recent ESVS guidelines [15]. On the other hand, the European Society of Cardiology Guidelines recommend that in patients with dissection, competitive sports and isometric heavy weightlifting should be discouraged to reduce aortic wall shear stress due to sudden rises in arterial blood pressure [12]. The American Heart Association Guidelines recommend restrictions not only on lifestyle activities, but also on certain work activities after a current or previously repaired aortic dissection. Future guidelines need to focus more on this important patient issue [49].

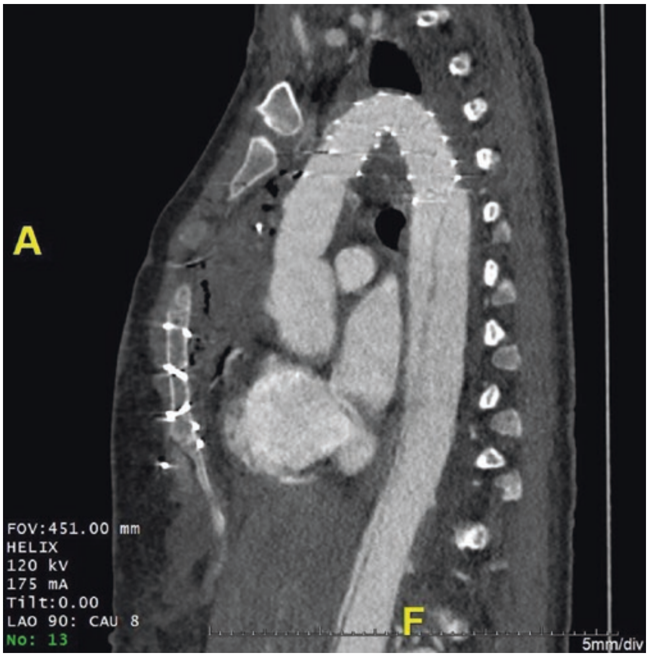

Fig. 54.9 Stent graft induced new entry (SINE)

Quality of Life (QOL)

It is important to highlight that the sudden change from being a ‘healthy’ individual to becoming a patient with a life threatening condition may have an impact on the quality of life. However, there is lack of evidence on this important issue. A Swedish study [50] has evaluated the QOL of patients with CTBAD. There were only minor differences in functioning and well-being between patients and the normal population. Patients reported similar emotional well-being, cognitive functioning, quality of sleep, overall general health and quality of social relations as their normal counterparts. However, patients’ perception of their current health, prior health, perceived resistance to illness and health concern was worse than in the normal population. Female patients also reported a lower satisfaction with their physical functioning than male patients or female counterparts in the normal population. Future studies evaluating outcomes of treatment of patients with CTBAD should also assess the impact of conservative and invasive treatments on QOL of these patients.

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55

Aortic Intramural Hematoma and Penetrating Aortic Ulcer

Abe DeAnda Jr. and Christine Shokrzadeh

High Yield Facts

- Intramural hematoma (IMH), penetrating aortic ulcer (PAU), and aortic dissection describe a spectrum of acute aortic syndrome.
- The pathophysiology of each process is not completely understood and there is significant overlap between each one.
- There is a predominance of men compared to women with dissection and the opposite in IMH and mixed dominance in PAU depending on location.
- Optimal medical management, open surgical repair, and endovascular approaches each have a role in the management of IMH and PAU.

Introduction

Acute aortic syndrome (AAS) describes a spectrum of aortic diseases, heterogeneous in their pathophysiology, prognosis, and outcome but similar in their clinical profile. This syndrome traditionally includes aortic dissection, intramural hematoma (IMH), and penetrating atherosclerotic aortic ulcer (PAU) [1]. It is the latter two conditions that are the subject of this chapter. As will be described, these specific entities will have overlap and associations, e.g. a PAU may lead into an IMH or dissection, IMH may degenerate into a dissection, etc. While the syndrome typically considers only the acute presentation of these entities, in some patients left untreated the disease will become chronic with associated changes in both the prognosis and treatment, thus both acute and chronic presentations will be discussed in this chapter. Acute aortic dissections are discussed in Chaps. 57 and 58, and chronic dissection in Chap. 59.

Pathophysiology

The development of IMH and PAU (and aortic dissections) is a complex interplay of atherosclerosis, media integrity, and the vasa vasorum (VV). The aortic media consists of 50–100 lamella and IMH tends to be located subadventitially in the outer third of the media similar to dissections in non-syndromic patients [2, 3] although when taken as an aggregate the medial tear in dissections appears closer to the intimal side [2]. PAU involves both the intima and media, and arises from an ulceration of an atherosclerotic plaque through the internal elastic lamina [4, 5] thus “penetrating” from the intima into the media (Fig. 55.1). The ulcer is frequently associated with IMH, development of an adventitial false aneurysm, transmural rupture, and may also be a nidus for the development of an aortic dissection [5] (Fig. 55.2).

One hypothesis for the development of IMH is rupture of the VV with subsequent intramural bleeding [6], supported by the observation that the region where IMH typically occurs corresponds to the pathway of the VV. Explanations as to why the VV would rupture in this region are unclear. The possibility that IMH is a dissection with an unappreciated intimal tear has also been suggested as an etiology [7]. In a small clinical series, Park et al. [8] demonstrated the majority of their patients with the diagnosis of IMH had some intimal lesion not previously seen on imaging but recognized on close inspection of the involved segment. Another study utilizing sub-millimeter spatial resolution contrast-enhanced multidetector computed tomography (MDCT) identified micro-intimal disruptions in 71% of 48 patients diagnosed with acute IMH [9].

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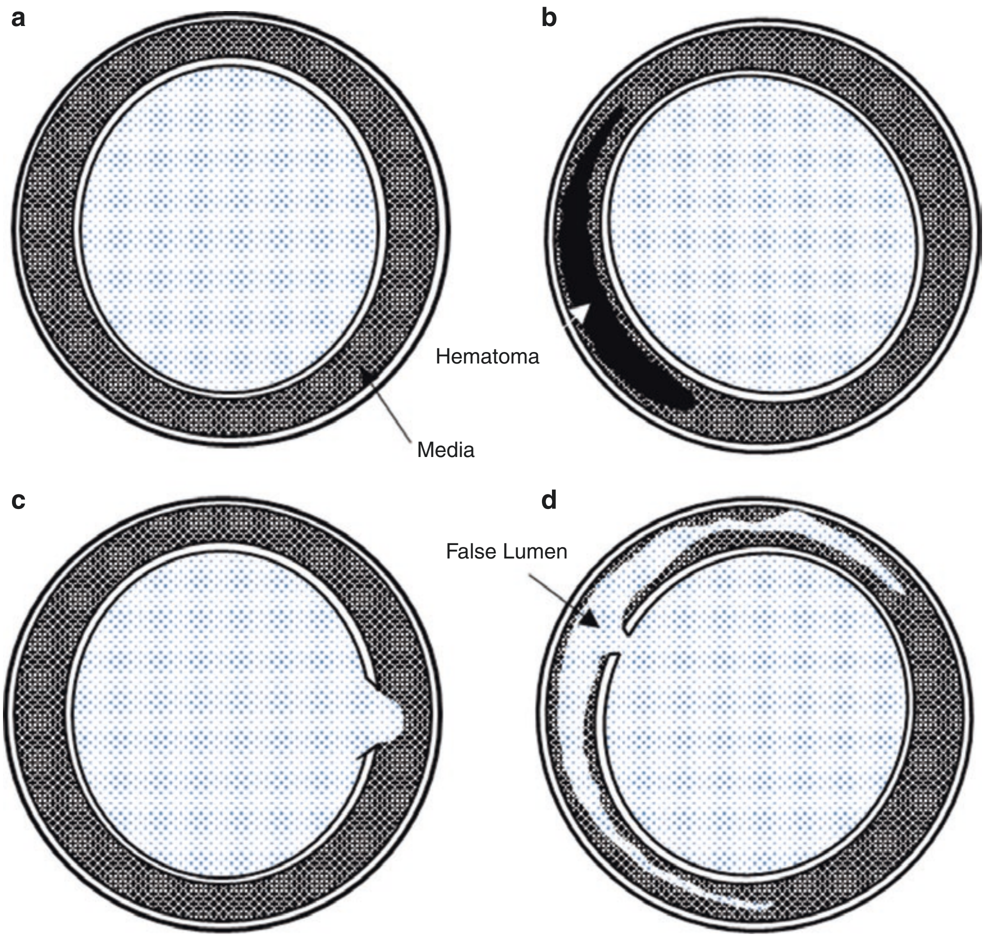

Fig. 55.1 Schematic of different extent of aortic syndromes. (**a**) Normal aorta. (**b**) Intramural hematoma. (**c**) Penetrating aortic ulcer. (**d**) Aortic dissection

IMH and PAU both occur in the setting of atherosclerosis. Haverich has presented an interesting "unifying theorem" to address the relationship between the VV and the development of atherosclerosis which has implications for the pathogenesis of both IMH and PAU with the observation that "…areas predictably spared from atherosclerosis often lack VV" [10]. The paradox here is that vessels are spared of atherosclerosis when the VV are absent [11], but when VV are present but *constricted*, those segments develop the characteristic fatty streaks that development into atherosclerotic lesions [12].

In a porcine model, Angouras et al. [13] interrupted the VV flow in the upper portion of the thoracic aorta and studied the involved segment 15 days later. Compared to controls, these segments demonstrated necrosis of the outer media as well as disruption of the architecture of the elastin and collagen fibers (without a corresponding change in content). This resulted in an increase in wall stiffness especially in the outer portion of the wall which in the setting of increased wall stress (as seen in arterial hypertension) or trauma could result in a medial tear and IMH [13].

Finally, combining observations of Park et al. [8] with the findings of Angouras et al. [13] another consideration is simply a flip of the paradigm, i.e. a dissection is IMH with an intimal tear, both processes start in the media but when the ischemic necrosis is closer to the intimal side the likelihood of egress through the lumen increases. This is supported by the observation that IMH can progress to a frank dissection but a dissection is not always accompanied by IMH.

Epidemiology

The true incidence of IMH is hampered by difficulties in definition. Described originally by Krukenberg as a "dissection without intimal tear" [14], as noted above there remains a school of thought that IMH is a dissection where the tear has not been identified and/or the false lumen of the dissection has thrombosed completely [8, 15]. Given the issues with defining IMH, there likely are instances where IMH is classified as an acute dissection (and treated accordingly). Additionally it has been suggested that the

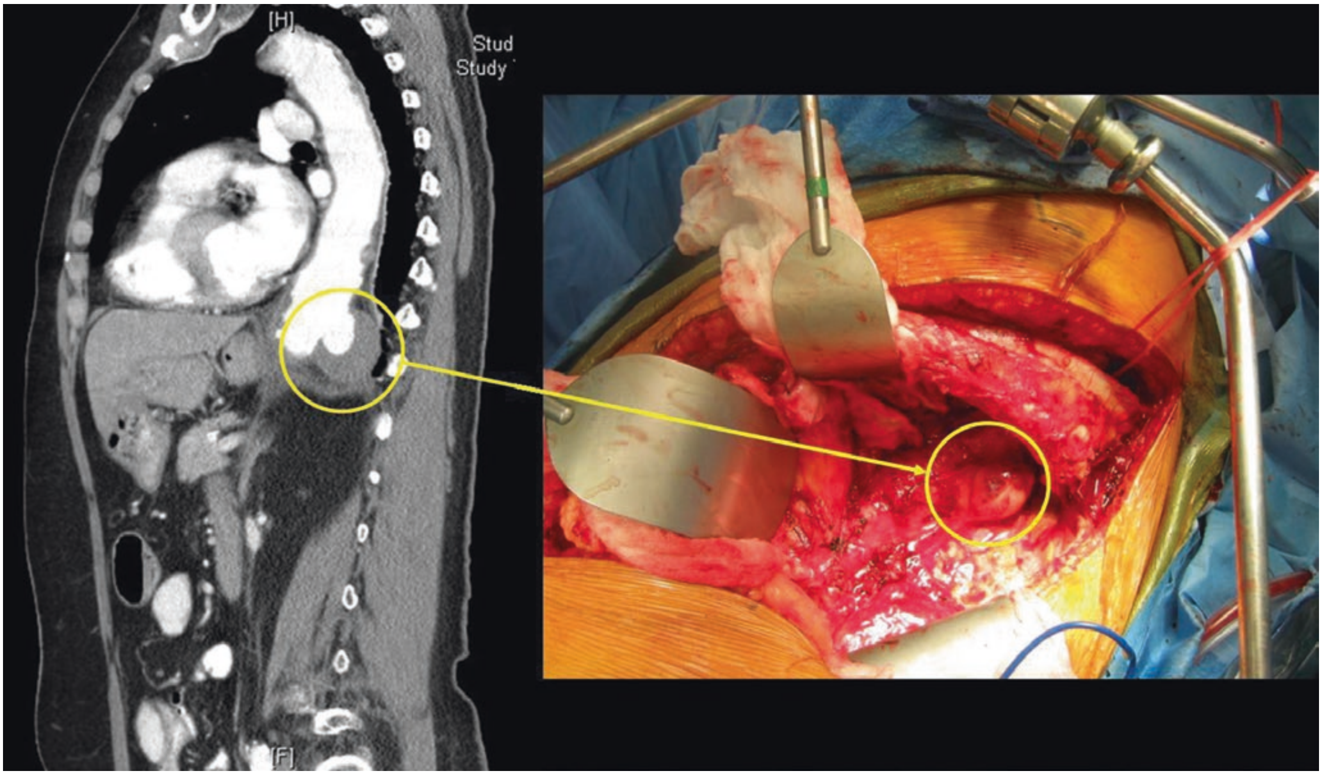

Fig. 55.2 Giant penetrating ulcer. CT scan (left) with intraoperative photograph of same lesion. (Photo courtesy of author AD)

lower incidence of IMH seen in tertiary centers (which are more likely to report to aortic clinical or administrative databases) may have evolved into a typical acute dissection by the time the patient arrived from the referring facility [16].

Generally in Western countries IMH accounts for approximately 10% of AAS, or 1–3 per 100,000 person-years [16]. Reports from Asian countries have noted rates of up to 30% of AAS [17] although recent papers have disputed this geographical difference. While there is an increased incidence of aortic dissection in men compared to women, there appears to be the opposite phenomenon with IMH with a slight predominance in women [18]. There is also a slight predominance of Type B IMH compared to Type A IMH (58% vs. 42%) which contrasts with classical aortic dissections where approximately one-third are Type B [16]. In comparison with dissections, patients with IMH tend to be older and are more likely to have hypertension [19]. There is no apparent association of IMH with Marfan syndrome or other connective tissue disorders [20].

The incidence of PAU is even more difficult to assign a number to since penetrating ulcers are often discovered incidentally, but in the setting of AAS it accounts for 2–7% of cases [21]. There is a slight predominance in men [22] but when separated between the thoracic and abdominal aorta, PAU is more common in women in the thoracic location and vice versa in the abdominal aorta [23]. Within the thoracic aorta (ascending and descending), PAU occurs in the descending thoracic aorta in 90% of patients [24]. As previously noted, disruption of the media can lead to the development of IMH, and more uncommonly frank aortic dissection thus being under-reported in settings where a more serious clinical issue is at hand. In the retrospective review by Coady et al., 15 of 198 (7.6%) patients treated for either Type A or B aortic dissections were found to have a PAU [22].

Clinical Features

Patients presenting with IMH and PAU have similar symptoms of those presenting with aortic dissections. IMH pain will typically depend on whether the ascending (Type A) or descending (Type B) is involved, but unlike aortic dissections the pain does not often radiate [19]. The physical examination may be unremarkable. For Type A IMH, malperfusion and aortic regurgitation are not as common as in dissection but cardiac tamponade is seen more frequently [25]. Pain may not be a component of PAU, 87% of patients in a Mayo Center study were asymptomatic at the time of diagnosis [23]. Importantly, it is the imaging features and not the clinical features that are critical for distinguishing one acute aortic syndrome from another.

Diagnosis

Work up of a patient with an AAS will have some overlap with the workup for an acute coronary syndrome. For Type A IMH the ECG is normal more frequently than with Type A dissection (47.6% vs. 30.7%, p = 0.005 [16]) and normal overall (Type A and B IMH) in 35–40% of patients [16, 26]. Chest radiography is abnormal but non-diagnostic in the majority of patients, with typical findings being an abnormal contour of the aorta or widened mediastinum [16, 26]. As in the case of classic aortic dissection, with IMH and PAU a high index of suspicion will frequently lead to further early imaging of the thoracic aorta with subsequent confirmation of the diagnosis.

Computed tomography (CT) has a high sensitivity and specificity in AAS with most series focusing on classic dissection. CT remains critical for the identification of both IMH and PAU with the caveat that subtleties with IMH exist (i.e. IMH best diagnosed with non-contrast study) (Fig. 55.3). The diagnosis of IMH requires the presence of thickening of the aortic wall >5 mm, either crescent shaped or circular, with no detectable blood flow [27]. The combination of CT imaging without contrast followed by contrast can yield sensitivities as high as 96% [28]. On CT, PAU is defined as a focal outpouching either through an area of intimal calcification or in an area free of intimal calcification but with diffuse atherosclerosis elsewhere [29]. On unenhanced CT, PAU make be mistaken for IMH but this is readily confirmed with contrast CT. In addition to the diagnostic utility of CT, prognostic information is also provided. Schlatter et al. noted that the presence of CT-measured intimal irregularities predicted progression of disease in 80% of patients with IMH [30], and Winnerkvist et al. showed a correlation of aortic diameter and progression of IMH [31]. Finally, if endovascular repair is being contemplated for either IMH or PAU a contrast CT scan is critical for preoperative planning.

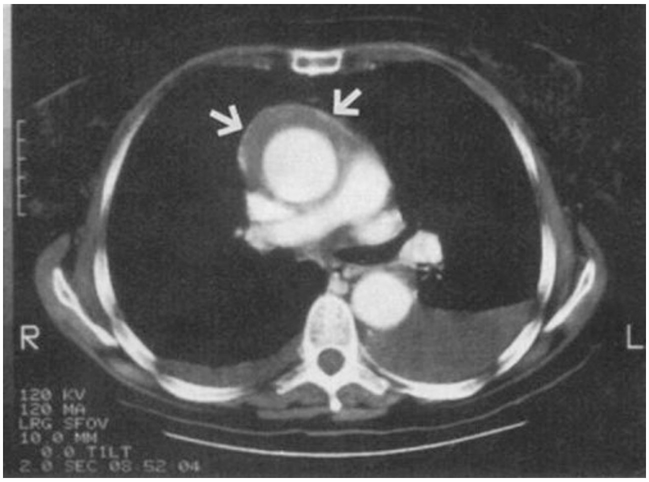

Fig. 55.3 CT scan of type A intramural hematoma

In some studies transesophageal echocardiography (TEE) has both a high sensitivity (100%) and specificity (91%) for IMH [32, 33], and in other studies shown to have a slightly lower sensitivity (90–100%) than transthoracic echocardiography (TTE) [34–36]. When the cut-off limit of 5 mm is used for the diagnosis of IMH, the sensitivity of TTE can drop to as low as 40%. It is for this reason that TTE is not recommended as the sole imaging technique to confirm IMH [27]. Both TTE and TEE can identify PAU but with lower sensitivity and specificity, and with the caveat that there will be anechoic regions or blind spots.

Treatment, Outcomes and Prognosis

Medical Management

Medical management of IMH is generally limited to the Type B dissection as the disease progression follows that of typical dissection in non-Asian series, i.e. outcomes favor operative management in Type A IMH and medical management in Type B IMH. Interestingly, Falconi et al. compared medical management vs. surgical management for Type B IMH and noted similar results in terms of mortality (19% vs. 17%, respectively) which historically is not true for Type B dissections. Using data from the International Registry of Acute Aortic Dissection (IRAD) and directly comparing Type B IMH to Type B dissections in terms of in-hospital mortality rates, Falconi et al. found the mortality rates for IMH to be statistically similar to Type B dissections (4.4% vs. 11.1%, p = 0.062) [26]. Of the patients followed in the IRAD database, almost 90% of Type B IMH patients were managed medically with the remainder evenly divided between open and endovascular surgery. Interestingly, compared to classic Type A dissection, more patients were handled medically with Type A IMH although the difference did not reach significance (15.6% vs. 11.9%) [16].

Anti-impulse therapy with selective beta-blockade is the standard therapy used in medical management of IMH. There is some disparity on the likelihood of resolution of the IMH spontaneously, and there appears to be geographical and cultural differences.

The predictors for complications in IMH include persistent pain despite optimal medical management, difficulty in managing blood pressure, Type A IMH, aortic diameter >50 mm, progressive maximum wall thickness >11 mm, enlarging aortic diameter, recurrent pleural effusion, PAU in the involved segment, and malperfusion [27].

PAU is frequently found incidentally and if asymptomatic may be managed medically with anti-impulse therapy and routine imaging. For asymptomatic large PAU, i.e. where the greatest diameter is >20 mm or the neck is >10 mm, early intervention has been suggested because of the higher risk of progression and rupture [37] but this approach has not been validated [21].

Open Surgical Repair

Type A IMH does not respond favorably to medical management, and at least for Western countries has mortality rates similar to Type A dissections. Because of this, emergency surgery is indicated with Type A IMH especially in the setting of a pericardial effusion, tamponade, ongoing pain, or large aneurysm [27]. In some patients, i.e. elderly or with significant co-morbidities, it is reasonable to attempt a period of medical optimization with the possibility of regression of the disease especially when the IMH is not associated with aneurysmal disease or the wall thickness is <11 mm [17, 38], but the majority of patients will require repair. Currently there are no accepted endovascular options for Type A IMH other than anecdotal reports. Open surgical repair proceeds similar to that typically done for classical Type A dissections with the understanding that as (by definition) there are no intimal tears involved, the extent of resection both proximally and distally requires the judgement of the surgeon i.e. "normal" aorta may not be found. Additionally, it is our practice and personal preference to perform these repairs under hypothermic circulatory arrest with ***no*** clamping of the aorta out of concern that the crossclamp may convert the IMH to a frank dissection upon release of the clamp, and that the distal anastomosis is best addressed open with removal of the "currant jelly" medial hematoma and repair of the wall prior to completing the anastomosis.

Type B IMH and PAU can both be approached with open surgical repair, and typically only the involved segment is resected and replaced with a prosthetic graft or homograft. For Type B IMH, as with Type A IMH, we prefer to avoid clamping the aorta proximally or distally out of concern of creating an intimal defect and subsequent conversion to frank dissection. Avoidance of clamping would therefore require a period of circulatory arrest.

Finally, for PAU, as this disease is associated with severe atherosclerosis, finding a normal segment of aorta proximally and distally to clamp and sew to might be difficult.

Endovascular Repair

While the open surgical approach to Type A IMH is well described and documented, the subtleties of Type B IMH in terms of predictability of disease progression and response to medical management have introduced some variation in practice. For uncomplicated Type B IMH, the European Consensus Guidelines recommend initial medical management with careful, repetitive surveillance and imaging (Class I recommendation) [27]. In the setting of continuing or recurrent pain, expansion of the hematoma, development of a periaortic hematoma, or conversion to a frank dissection these same guidelines recommend either TEVAR (Class IIa recommendation) or open repair (Class IIb recommendation) [27]. These same recommendations are made for PAU (Fig. 55.4).

Li et al. conducted a prospective study of endovascular repair of acute Type B IMH and in a comparison of 33 patients treated with TEVAR and 23 patients treated with medical therapy, showed no progression of the IMH or mortality in the endovascular repair group. In addition, the endovascular group was also shown to have reduced IMH dimensions after the procedure. The authors claim that without any treatment, 43% of type B IMH will progress to dis-

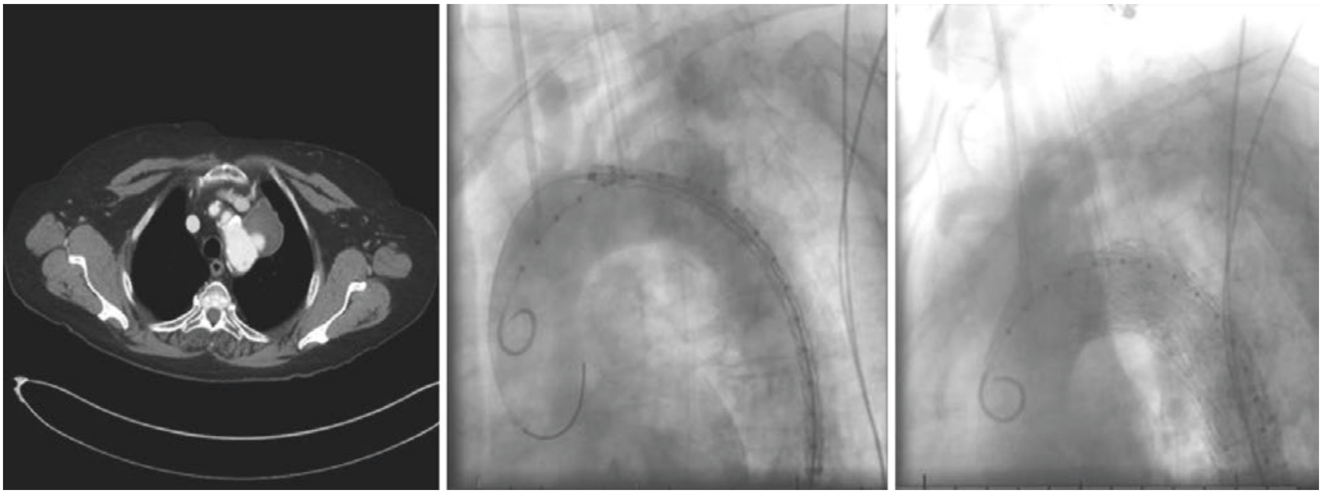

Fig. 55.4 Penetrating aortic ulcer (PAU) of proximal descending thoracic aorta (left), with angiography pre- (center) and post- (right) stent graft. Note the local atherosclerosis near the PAU

section or rupture according to contemporary studies, especially in IMH with features of PAU, aortic aneurysm, large hematoma (>10 mm), and persistent pain [39]. This is in contrast to the medical therapy results seen in the IRAD data [26, 27]. In a similar prospective non-randomized study, Bischoff et al. divided patients into a best medical therapy group and a TEVAR group. Of the 28 patients in the TEVAR group, seven were immediately treated because of pain and imaging results, the remainder were treated because of clinical or radiological progression [40]. Early and late mortality were not significantly different between the TEVAR and medical management group and remarkably the incidence of complete remodeling (25%) and regression (75%) were nearly identical between the two groups. The authors noted that TEVAR in "…complicated IMHB [intramural hematoma type B] is feasible but associated with a substantial aortic reintervention rate" [40]. Given the near identical results, this would suggest that TEVAR might be reserved for complicated IMH only.

Pauls et al. showed 0% mortality in both the 30-day period follow up and at 3 years and a 0% rate of paralysis in their cohort of patients who received endovascular repair of symptomatic PAU [41].

In a systematic review and meta-analysis of TEVAR vs. open surgical repair of descending thoracic aortic disease, Cheng et al. showed an overall reduction in perioperative complications with TEVAR with a decrease in 30-day mortality and paraplegia in TEVAR compared to open surgery [42]. The limitations of the study included a heterogeneous group of pathologies including thoracic aortic aneurysms, dissections, rupture, trauma, IMH and PAU, as well as an appreciation that a medical management arm (for the IMH, PAU and uncomplicated dissections) was not included [42]. Contemporary data is still lacking on the long term benefit of endovascular repair of PAU and IMH. Current indications for TEVAR in IMH include the same indications as open surgery, i.e. disease progression or evolving complications such as dissection, rupture or persistent symptoms. Grimm et al. recommended long stent graft usage (>20 cm) for effective coverage of intimal disruption, and in their eight patients described, targeted a proximal area of presumed intimal rupture [43]. Finally, limited data have shown encouraging results of TEVAR for PAU patients who have progressed to pseudoaneurysm formation or rupture and thus supporting its use in these symptomatic patients [21].

For endovascular repair of IMH or PAU, computed tomographic angiogram (CTA) is the imaging of choice for pre-operative planning. Magnetic resonance angiography (MRA) is used in patients with severe iodine contrast allergy, renal disease or pregnancy. However MRA offers less spatial resolution than CTA and its sensitivity to metal can produce greater imaging artifacts that render the study less ideal. High resolution CTA allows for reconstruction of the aorta in 3D and its branches for assessment of angulation, profile and positioning of stent graft. Appropriate diameter and length of the aorta are required for safe deployment of the aortic stent graft. The part of the aorta distal to the left common carotid artery and proximal to the distal end of the left subclavian artery provides the most stable proximal landing zone. To extend the proximal landing zone, carotid-subclavian bypass or other bypass strategies such as carotid-carotid bypass and carotid-axillary bypass can be utilized prior to TEVAR. The left subclavian artery is routinely covered by the stent graft during TEVAR in our practice with low rate of complication. Indications for left carotid-subclavian bypass include presence of coronary artery bypass using left internal mammary artery, dominate left vertebral artery confirmed on arteriography, right subclavian artery or innominate artery stenosis, aberrant origin of left vertebral artery, left brachial artery occlusion, aberrant right subclavian artery origin distal to the left subclavian artery, left or right vertebral artery terminating in PICA, presence of an arteriovenous fistula or graft in the left arm for hemodialysis [44]. The distal landing zone's landmark is the celiac artery. Ideally, the proximal and distal landing zones should be 2 cm in length and free of calcification and thrombus to ensure adequate seal. Stent grafts are usually oversized by 10–20% in relation to the native aortic diameter. In addition, examining the iliofemoral vasculature with appropriate imaging is also important in perioperative planning for TEVAR. Tortuous, small diameter and heavy calcification of the iliofemoral vessels would warrant iliac artery conduit. Endovascular repair is recommended in IMH with an associated PAU, progression to dissection, or a discrete leakage site seen on CTA [45]. Extensive atherosclerosis of the aorta is often present with PAU which makes endovascular repair challenging if the atherosclerotic disease extends to the peripheral arteries. Furthermore, presence of laminated thrombus associated with PAU poses another challenge for achieving adequate landing zone for TEVAR [45].

Depending on the patient population, either general anesthesia or monitored sedation is utilized during endovascular repair of IMH or PAU. We routinely place a spinal drain prior to patients undergoing TEVAR to minimize risk of paralysis, although the documented risk of paraplegia with short segment entry point coverage with IMH is low at less than 2% [46]. An additional strategy to reduce the risk of paraplegia includes limiting stent graft coverage of the thoracic aorta to 15–20 cm, to reduce over-coverage of intercostal vessels.

Conclusion

IMH and PAU make up a small but significant portion of AAS, and can occur together or isolated, as well as in conjunction with aortic dissections. The prompt recognition of the process is critical in the development of a therapeutic plan of attack. Optimal medical management, open surgery, and endovascular surgery each play a role in the treatment of these processes highlighting the importance of individualizing the approach to each patient.

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Descending Thoracic and Thoracoabdominal Aortic Aneurysms

56

Konstadinos A. Plestis, Oleg I. Orlov, Vishal N. Shah,
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High Yield Facts

- Descending thoracic (DTAA) and thoracoabdominal aortic aneurysms (TAAA), although usually asymptomatic, are lethal diseases requiring urgent attention.
- The clinical progression of an aortic aneurysm is continued expansion and eventual rupture.
- Aneurysm size is the most accepted factor in establishing the timing of elective repair.
- Computed tomography (CT) and magnetic resonance imaging (MRI) are the most commonly used diagnostic tools to detect DTAA and TAAA and determine risk for future complications.
- Open repair still remains the gold standard treatment for DTAA and TAAA.
- Distal aortic perfusion, cerebrospinal fluid drainage and selective visceral and renal artery perfusion are important adjuncts in preventing paraplegia and end-organ ischemia.
- Deep hypothermic circulatory arrest is an important technique when proximal clamping is not feasible.
- Acceptable rates of mortality, paraplegia, stroke and renal insufficiency can be achieved using these specialized techniques.

Introduction

The main goal of the diagnosis and treatment of aortic aneurysm is to prevent rupture. Progress in cerebral, spinal cord, and visceral protection during complex descending thoracic (DTAA) and thoracoabdominal aortic aneurysms (TAAA) repair has led to a significant decrease in morbidity and mortality. This chapter encompasses the authors' experience in the management of DTAAs and TAAAs, focusing on critical steps and adjunctive techniques during open repair.

Etiology

The majority of DTAAs and TAAAs are degenerative in etiology and associated with atherosclerosis or chronic dissection. Their incidence is equally distributed in sporadic and familial cases. Other etiologies are included in Table 56.1.

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Epidemiology, Clinical Presentation and Natural History

The incidence of aortic aneurysms is approximately 1 in 10,000 people. Of all thoracic aorta aneurysms, DTAAs and TAAAs account for 45% and 5% of cases respectively [1, 2]. Patients with aneurysms generally present without symptoms or with vague, nonspecific pain, or seldom with symptoms of local compression (dysphagia, stridor). Usually, a ripping sensation radiating to the back is associated with dissection.

The cumulative lifetime risk of rupture, dissection and death is 43% for DTAA and TAAA greater than 7 cm in maximum diameter (Fig. 56.1) [3]. Also, the annual risk of the same endpoints is 15.6% for aneurysms that exceed 6 cm in maximum diameter (Fig. 56.2). The poor prognosis after rupture foretells the importance of intervention before dissection occurs.

Table 56.1 Etiologies of thoracic aortic aneurysms

Aneurysm	1. Chronic aortic dissection 2. Atherosclerosis 3. Degenerative: Cystic medial degeneration 4. Congenital: Marfan Syndrome, Ehlers-Danlos Syndrome, Loeys-Dietz Syndrome 5. Chronic posttraumatic
Ulcer	Penetrating and atherosclerotic
Inflammatory disease	Takayasu arteritis, Behcet disease, Kawasaki disease, Giant cell arteritis, ankylosing spondylitis
Traumatic aneurysm	Blunt trauma
Post-operative complications	Endoleak

Diagnosis of DTAA and TAAA

Computed tomography (CT) and magnetic resonance imaging (MRI) are the most commonly used diagnostic imaging modalities (Table 56.2). For measurements taken by CT or MRI, the external diameter should be measured perpendicular to the axis of blood flow [4]. Of note, for measurements taken by echocardiography, the internal diameter is typically measured perpendicular to the axis of blood flow.

The classification of DTAA and TAAA is essential to determine the risk of paraplegia and mortality (Figs. 56.3 and 56.4). In general, the descending thoracic aortic aneurysms are classified based on extent and location of the aneurysms. For TAAA, the Crawford/ Safi classification is used. Extents II and III TAAA are associated with the highest incidence of mortality and paraplegia [5].

Treatment Options

Medical

Optimal management of risk factors is important to reduce expansion, dissection, or rupture of an aneurysm. Control of blood pressure and hyperlipidemia should be advised along with smoking cessation.

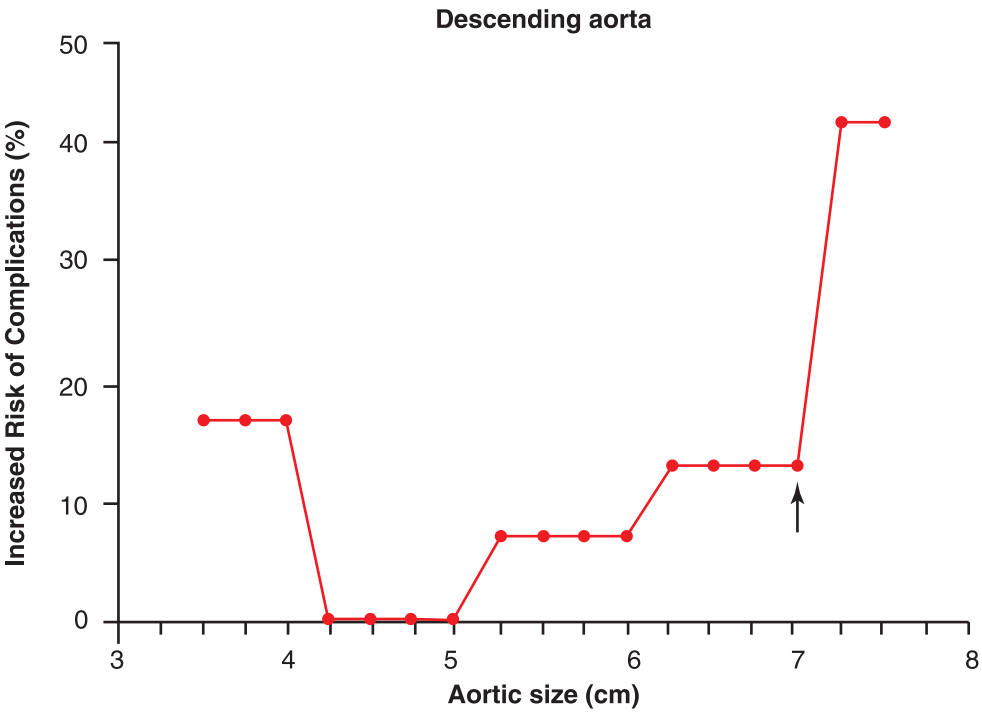

Fig. 56.1 The cumulative lifetime risk of rupture, dissection, and death is directly related to the DTAA or TAAA size [3]

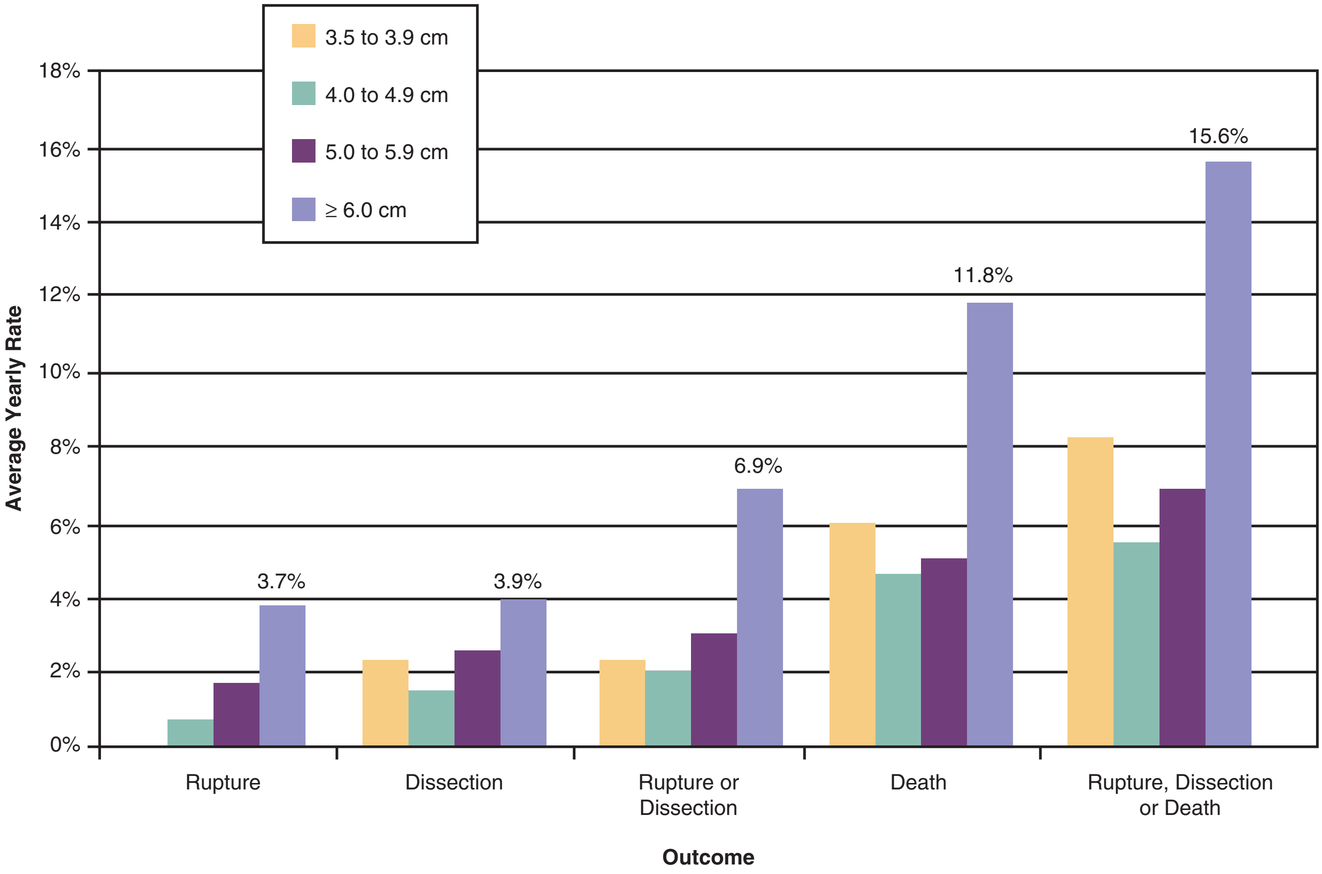

Fig. 56.2 The average yearly rate of rupture, dissection or death based on aneurysm size [3]

Table 56.2 Diagnosis of aortic aneurysms

	Advantages	Disadvantages
CT (most common)	Non-invasive, visualization of aortic wall, aortic size, presence of clot	Effect of ionizing radiation and contrast media on renal function
MRI	No ionizing radiation used	Time consuming, claustrophobia, contraindicated in patients with clips and some mechanical valves
Echocardiography (TTE, TEE)	View of ascending and descending aorta, evaluation of heart and valvular function	Invasive, need for sedation and intubation
Angiography	Localization of aneurysms, presence of aortic regurgitation	Invasive, underestimates the size of large aneurysms, contrast medium anaphylaxis, worsening effect on renal function

TTE transthoracic echocardiography, *TEE* transesophageal echocardiography

Endovascular Treatment

The issue of endovascular treatment is addressed in another chapter. Briefly, thoracic endovascular aortic repair (TEVAR) is indicated when aneurysmal size reaches a diameter of 5.5 cm preferably without involvement of visceral or renal branches. Endovascular treatment presents an attractive option for older and frailer patients as well as in cases of rupture [6, 7]. The use of endovascular stenting is discouraged in patients with connective tissue disorders.

In terms of deliverability of the endovascular graft, the diameter of the iliac artery, tortuosity, and degree of calcification of the iliofemoral anatomy should be assessed with CT angiography. The proximal landing zone is considered adequate at 2 cm in length, and devices are available from 22 to 46 mm in diameter. Distal landing zone of 1–2 cm in length is acceptable.

Open Surgical Treatment

Open surgical treatment is indicated when DTAAs and TAAAs exceed 6.0 cm, if there is rapid growth (>0.5 cm/year), or if the patient is symptomatic.

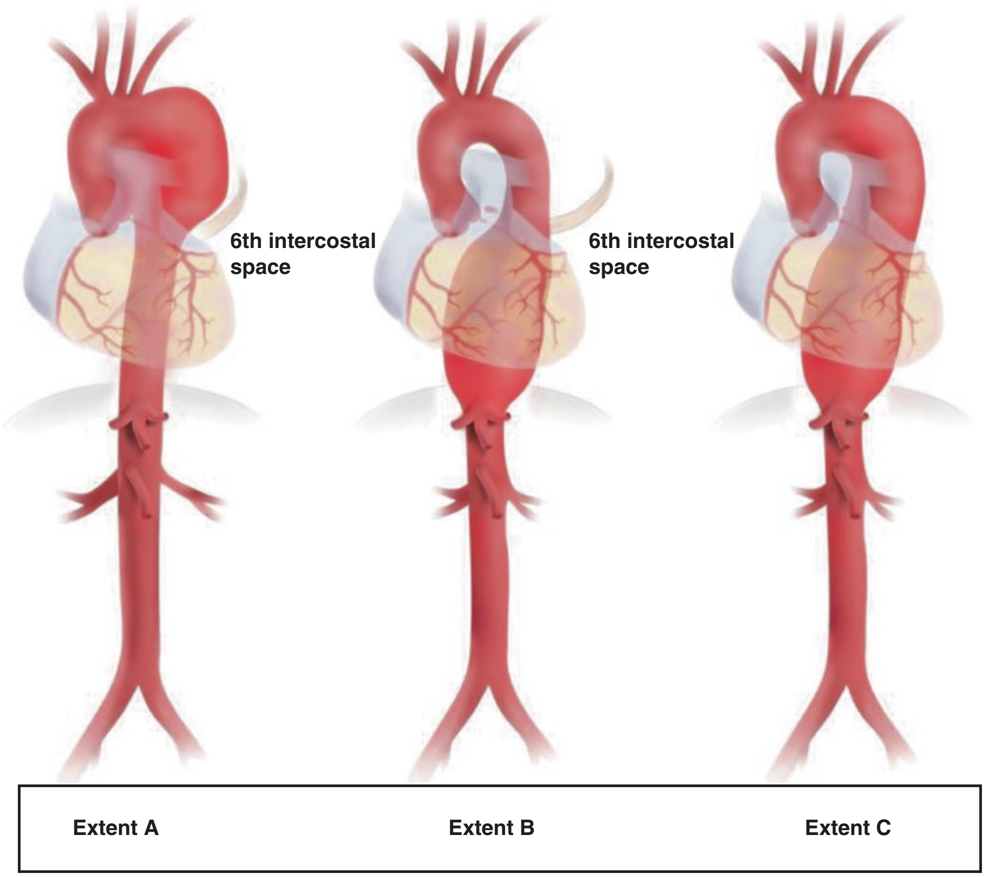
6th intercostal space
6th intercostal space
Extent A
Extent B
Extent C

Fig. 56.3 Classification of descending thoracic aortic aneurysms. Extent A: Aneurysm extending from the distal origin of the left subclavian artery to the sixth intercostal space. Extent B: Aneurysm extending from T6 to T12. Extent C: Aneurysm of entire DTA from the left subclavian artery to T12

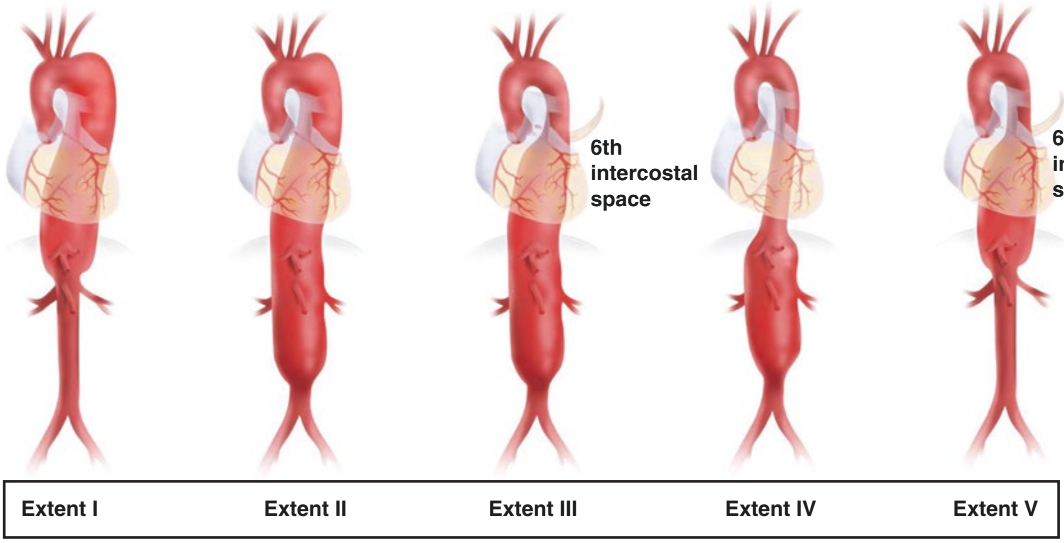
6th intercostal space
6th intercostal space
Extent I
Extent II
Extent III
Extent IV
Extent V

Fig. 56.4 Classification of thoracoabdominal aortic aneurysms. Extent I: From left subclavian to above the most proximal renal artery. Extent II: From left subclavian to below the renal artery. Extent III: From T6 to below the renal arteries. Extent IV: From T12 to below the renal arteries. Extent V: From T6 to just above the renal arteries

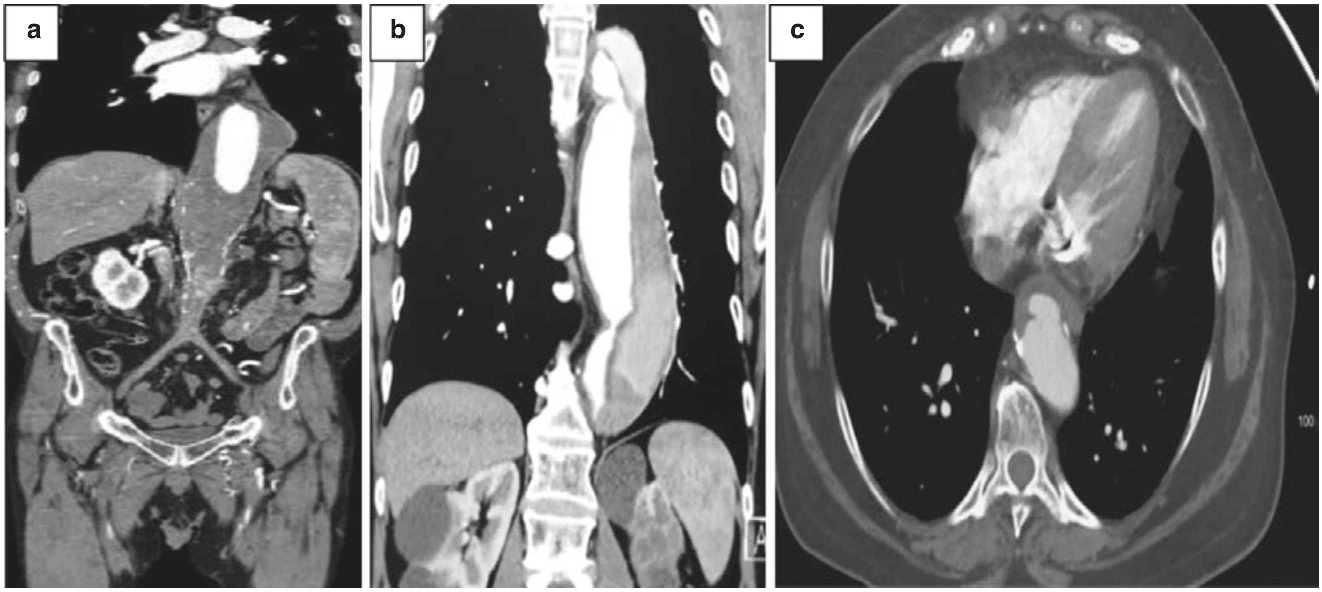

Fig. 56.5 (**a**) Atherosclerotic aortic aneurysm with infradiaphragmatic occlusion of the aorta and iliac arteries. (**b**) Aneurysmal dilation of thoracoabdominal aorta secondary to chronic dissection. (**c**) Penetrating ulcer

Table 56.3 Preoperative testing in open repair of DTAA and TAAA

Laboratory work	Creatinine Glomerular filtration rate Liver enzymes Complete Blood Count Prothrombin time/International normalized ratio
Pulmonary function testing	Forced expiratory volume in 1 s Forced vital capacity
CT coronary angiography	Coronary disease and anatomy
Echocardiography	Left ventricular function Aortic valve insufficiency

Preoperative Planning and Set-Up

A thorough history and physical examination should be performed. Kidney function, liver enzymes and routine blood work are evaluated. Pulmonary function testing and conventional or CT coronary angiography are performed in all patients. Echocardiographic assessment of left ventricular function and aortic valve insufficiency is performed. CT angiography evaluates operative anatomy, specifically the spatial relationships and the presence of significant atherosclerotic disease among the visceral and renal arteries (Fig. 56.5). Suitable cannulation and proximal clamp sites are identified on CT angiography. Evaluation of the aorta for luminal thrombus, atheroma, and calcification is crucial for operative planning (Table 56.3).

In the operating room, induction of general endotracheal anesthesia is performed with a double lumen tube for selective right lung ventilation. Left and right radial and femoral arterial lines are inserted. The patient is positioned in the modified right lateral decubitus position with the left hip rotated at 30° to the operating table in order to access both femoral arteries and veins. The upper body is rotated at 60°, and the left hand is placed above the patient's head (Fig. 56.6).

Cerebrospinal Fluid Drainage

A catheter is introduced into the L4 and L5 space for drainage of cerebrospinal fluid (CSF) and capped the day before operation. Bloody CSF would warrant a delay in the procedure. CSF drainage is initiated after aortic cross-clamping with a maximum drainage rate of 10 cc/h and maintaining CSF pressure less than 10 mmHg [8]. Drainage is continued for 72 h postoperatively. If the patient develops spinal cord ischemia postoperatively, a maximum of 20 cc/h of CSF should be drained while maintaining a mean arterial pressure between 90 and 100 mmHg to increase the spinal cord perfusion pressure.

Incision

If the disease is limited to the descending aorta, a left posterolateral thoracotomy is performed. The chest is entered through the fifth or sixth intercostal space. A standard S-shaped thoracoabdominal incision is made for extent I, II, and III TAAAs. The sixth rib can be divided if necessary close to the spine and sternum to improve access to the proximal aorta. In Extent IV TAAA, the chest is entered through the seventh intercostal space since proximal aortic access is not mandatory. The incision is extended to the pubic symphysis. The left costal margin is transected. The diaphragm is

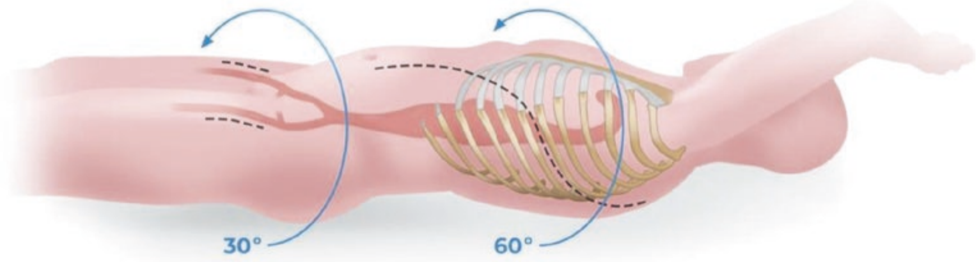

Fig. 56.6 Optimal patient positioning to allow for left S-shaped thoracoabdominal incision and bilateral groin exposure

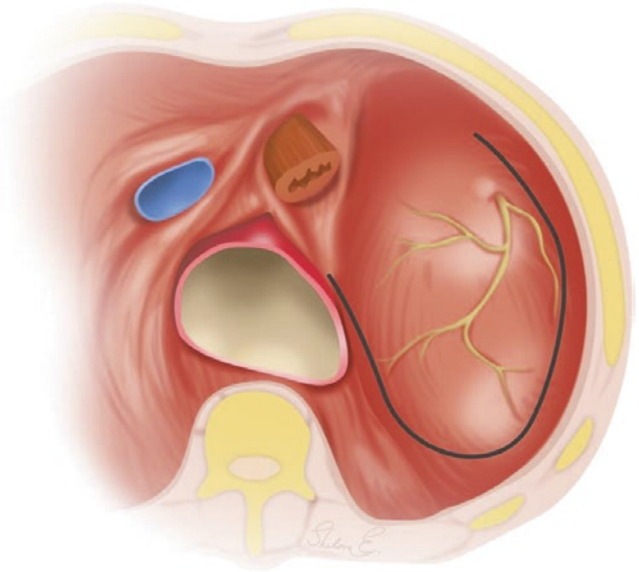

Fig. 56.7 The diaphragm is divided with a vascular stapler circumferentially leaving 3 cm of peripheral margin to avoid the main branches of the phrenic nerve and facilitate subsequent closure

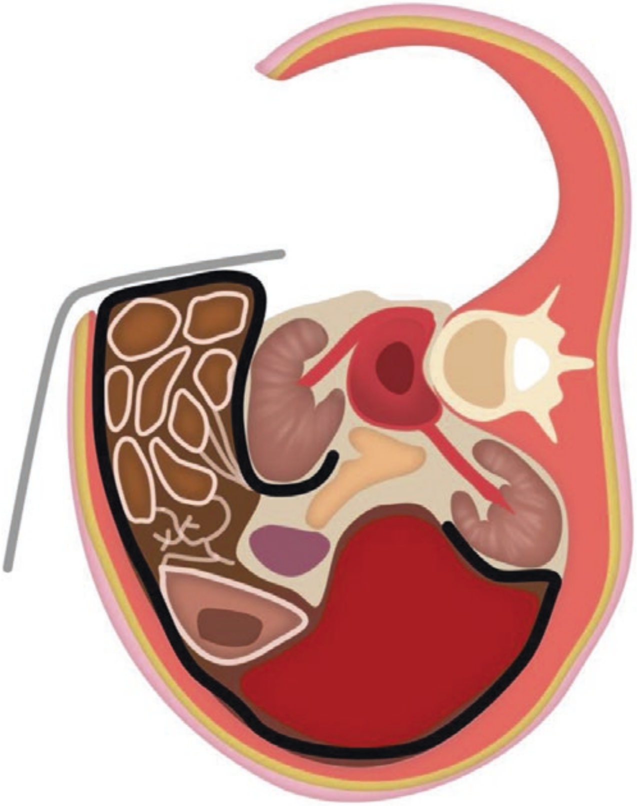

Fig. 56.8 The infradiaphragmatic aorta is exposed using a left-to-right medial visceral rotation

divided with a vascular stapler circumferentially leaving 3 cm of peripheral margin to facilitate closure (Fig. 56.7). The abdominal incision is tailored to accommodate the extent of the aortic aneurysm. The infradiaphragmatic aorta is exposed through a retroperitoneal approach which minimizes injury to intraperitoneal organs. The stomach, intestines, spleen and left kidney are retracted anteriorly by entering the avascular retroperitoneal space (Fig. 56.8). The left crus of the diaphragm is divided, and the infradiaphragmatic aorta is exposed. The left renal artery is identified. Care must be taken to avoid injury to a retro-aortic left renal vein which occurs in 2–3% of the population [9]. All lymphatics are clipped to avoid chyloperitoneum.

Cardiopulmonary Bypass

Cannulation Techniques

Intravenous heparin (3 mg/kg) is administered. Long venous cannula (28–34 F) (Bio-Medicus, Medtronic, Inc. Minneapolis, MN) is inserted through the left common femoral vein and advanced to the superior vena cava using the Seldinger technique under transesophageal (TEE) guidance (Video 56.1). Arterial cannulation is established via the left femoral artery using the Seldinger technique under TEE guidance. Alternatively, the right common femoral artery or the aorta distal to the cross-clamp can be used for distal aortic perfusion (Fig. 56.9).

Partial Cardiopulmonary Bypass (Distal Aortic Perfusion)

In cases of distal aortic perfusion, a cardiopulmonary bypass (CPB) circuit including centrifugal pump, reservoir, oxygenator and heat exchanger are used to establish flows of 2.0–2.5 L/min. This approach provides adequate blood oxygenation, permits collection of all shed blood into the perfusion circuit and enables quick conversion to full cardiopulmonary bypass in the event of hemodynamic instability.

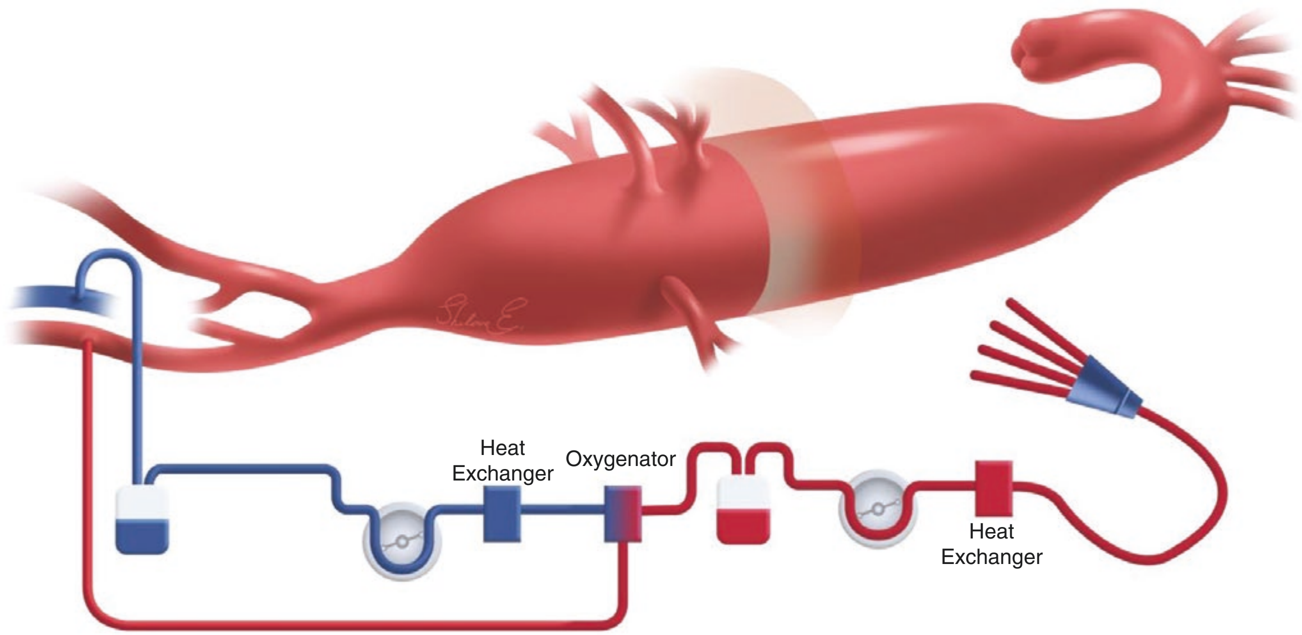

Fig. 56.9 The cardiopulmonary bypass circuit includes the venous reservoir, centrifugal pump with in-line heat exchanger and oxygenator. Note that a separate centrifugal pump is used for renal and visceral perfusion with an octopus system

Maintaining proximal systolic pressures of 110–130 mmHg is crucial for brain perfusion. Maintaining distal pressure of 60 mmHg is essential for spinal cord perfusion via the collateral network. Permissive mild hypothermia (32–34 °C, bladder) is routinely used since it is neuroprotective [10]. If necessary, the celiac axis, superior mesenteric artery and renal arteries are perfused with blood from the pump at a rate of 200–300 cc/min using balloon-tipped catheters.

Partial Left Heart Bypass (Distal Aortic Perfusion)

Another option for distal aortic perfusion is left atrial-femoral bypass by cannulating the left inferior pulmonary vein or the left atrial appendage and the left common femoral artery or distal aorta. A lower dose of intravenous heparin (1 mg/kg) is administered. A closed-circuit with an in-line centrifugal pump without cardiotomy reservoir, oxygenator or heater-cooler device (Bio-Medicus, Medtronic, Inc., Minneapolis, MN) is used to deliver oxygenated flows varying from 1.5 to 2.5 L/min.

Full Cardiopulmonary Bypass

In cases when clamping of the proximal aorta is not feasible, full CPB is used to establish circulatory arrest [10]. Cannulation strategies are previously described. If necessary, optimization of venous drainage can be achieved by direct cannulation of the pulmonary artery or the right atrium after the pericardium is opened. In the presence of extensive descending aorta atherosclerosis or iliofemoral disease, the ascending aorta is cannulated using the Seldinger technique under TEE guidance (Fig. 56.10) (Video 56.2). The right or left axillary arteries can be used for proximal perfusion in selective circumstances.

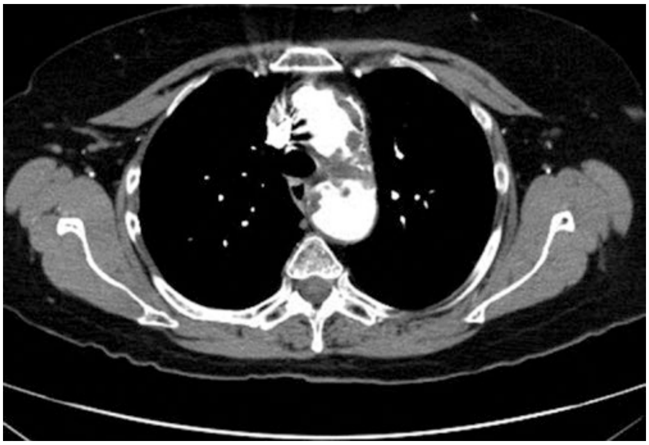

Fig. 56.10 Grade 5 aortic arch precludes proximal clamping of the aorta and requires circulatory arrest

Deep Hypothermic Circulatory Arrest

Deep hypothermic circulatory arrest (DHCA) is used when clamping of the proximal aorta is not safe or feasible. Adequate cerebral cooling is assured by jugular venous saturation higher than 95%, an esophageal temperature of 12–15 °C, or a bladder temperature of 20–22 °C. Cooling is continued for a minimum of 30 min. The left heart is vented through a catheter placed either through the left pulmonary vein or left ventricular apex. Prior to circulatory arrest, one dose of methylprednisolone (7 mg/kg) is administered to reduce spinal cord edema, and the head is packed in ice. Three additional doses of methylprednisolone are administered every 8 h postoperatively. Cerebral ischemic time of 30–40 min is adequate for construction of the proximal anastomosis. Upon achieving adequate hypothermia, the patient is placed in Trendelenburg position, and the vent is clamped to prevent suction of air into the heart. After construction of the proximal anastomosis, 2–3 min of total body retrograde venous perfusion at a rate of 1.5–2 L/min is used to de-air the ascending aorta and aortic arch. The arterial line is inserted into the graft and perfusion to the upper body is restored (Video 56.3). If possible, the aorta distal to the diseased segment is clamped to allow perfusion of the common iliac and hypogastric arteries, which are important collaterals to the spinal cord. After completion of the procedure, warming is carried out with the gradient between the esophageal and blood temperature maintained at less than 10 °C. Warming is usually accomplished within 1–1.5 h and maintained until the esophageal temperature reaches 35 °C and bladder temperature is higher than 33 °C. During the last 15–20 min, partial bypass is frequently utilized to take advantage of improved warming with pulsatile perfusion.

TAAA Repair Technique

Here, we describe our preferred technique for TAAA repair particularly for extents I, II, III, and V.

The left lung is collapsed and gently retracted to minimize injury. The left vagus and left recurrent laryngeal nerves are identified and dissected free from surrounding tissues. When distal aortic perfusion is utilized, the proximal descending aorta is clamped just below the left subclavian artery and in a suitable segment of the mid or distal descending aorta. In selective circumstances, the clamp can be placed between the left carotid and left subclavian arteries. Distal aortic perfusion is initiated at 1.5–2.5 L/min maintaining a mean distal pressure of 60 mmHg. CSF is drained at a maximum rate of 10 cc/h. The aorta is then opened between the clamps and the proximal aortic cuff is prepared by separating the aorta from the esophagus. The proximal anastomosis is completed (Fig. 56.11). All intercostal arteries are ligated. The pump is suspended and the distal clamp is removed. Upper intercostal arteries down to the level of T6 level are ligated to avoid back-bleeding and potential steal from the spinal cord (Video 56.2). Back-bleeding from large patent intercostal arteries between T7 and L1 is temporarily controlled with fine Fogarty catheters (Fig. 56.12) (Video 56.4).

Pruitt catheters are inserted into the ostia of celiac axis, superior mesenteric artery, and right and left renal arteries to perfuse the visceral vessels with the blood from the pump at a rate of 250–300 cc/min (Fig. 56.13). The distal anastomosis is then completed, the graft is de-aired and distal perfusion is initiated. Reimplantation of the celiac axis, superior mesenteric artery, and right and left renal arteries is accomplished using a trifurcated 14 by 10 mm or 12 by 8 mm Dacron graft. The larger limb of the trifurcated graft is beveled and anastomosed around the celiac axis, superior mesenteric artery and right renal artery with running 5–0 Prolene® suture, taking care not to displace the perfusion catheters (Fig. 56.14).

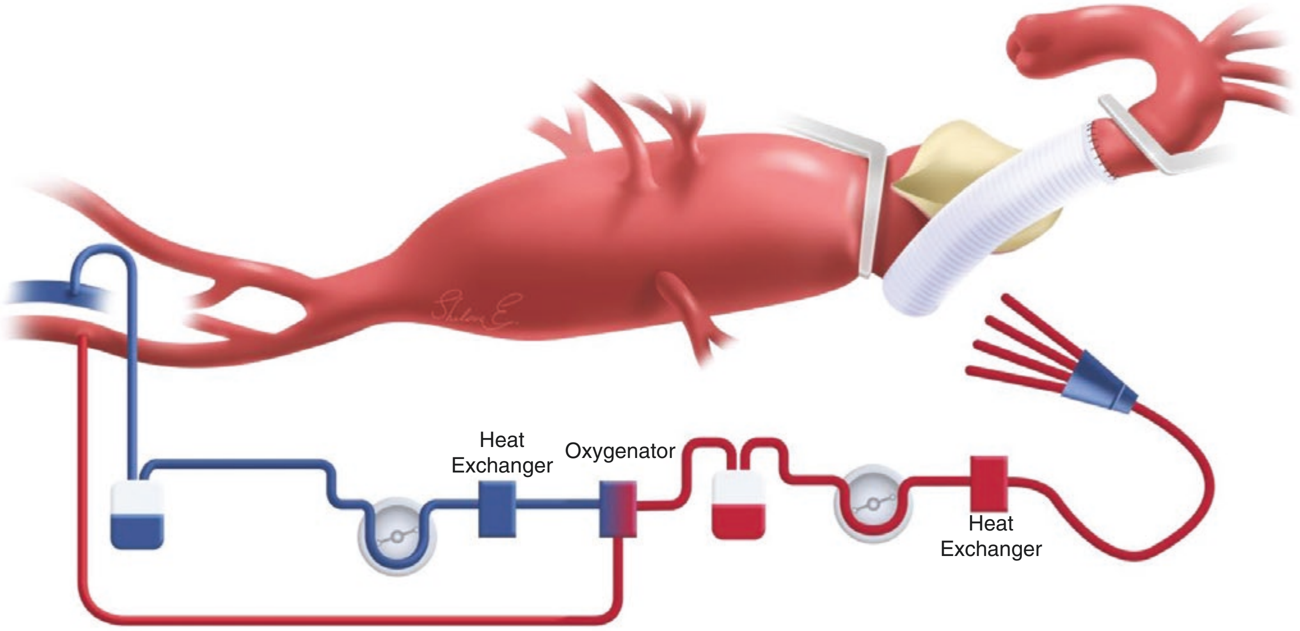

Fig. 56.11 Note the position of the clamps on the aorta. The proximal aorta is opened, and the proximal anastomosis is completed

The second limb is anastomosed to the left renal artery in an end-to-end fashion using 5–0 Prolene suture. Subsequently, the catheter is inserted directly into the main limb of the trifurcation graft to continue end-organ perfusion (Fig. 56.15). Alternatively, a graft with four branches can be used (Fig. 56.16), which is preferred in patients with connective tissue disorders by eliminating all pathologic tissue and preventing a patch aneurysm. Back-bleeding of T7–L1 intercostal arteries is assessed by removing the small Fogarty catheters. If back-bleeding is brisk, we may not reimplant any intercostal arteries [11]. Consideration is given to reimplant patent intercostal arteries if back-bleeding is poor, the patient has prior abdominal aorta replacement, there is occlusion of the hypogastric arteries, or an aneurysm is extensive (Extent II). Patent intercostal arteries are reimplanted into the Dacron tube graft using an island technique. Subsequently, the proximal and distal grafts are anastomosed to each other in an end-to-end fashion. The main limb is then attached in an end-to-side fashion to the main graft. All clamps are removed, antegrade flow is established and the pump is stopped (Fig. 56.17).

In some cases particularly during extent I TAAA repair, the graft can be beveled and anastomosed around the celiac axis, superior mesenteric artery, and right renal artery.

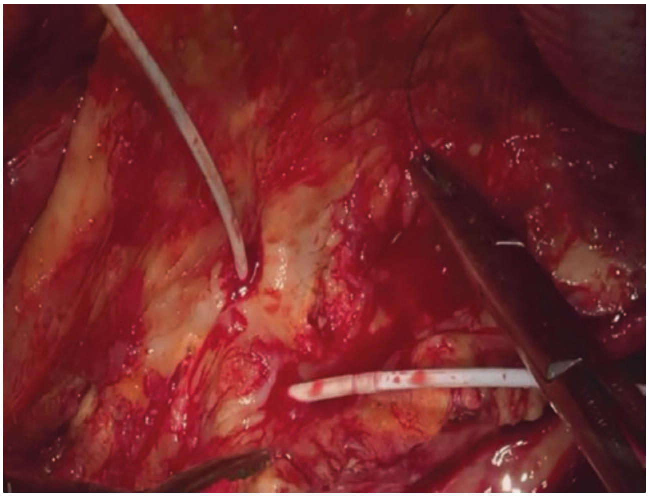

Fig. 56.12 Small Fogarty catheters occlude lower thoracic and upper lumbar intercostal arteries

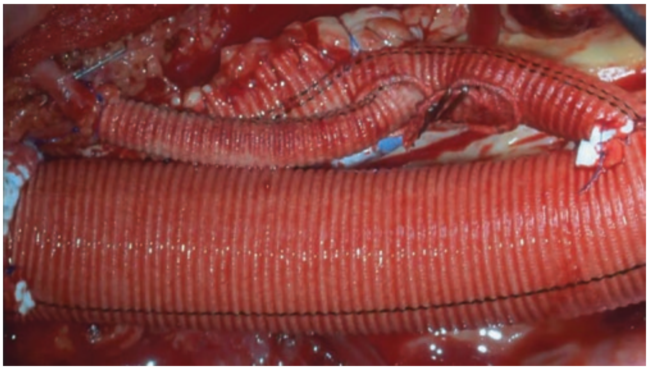

Fig. 56.14 The main limb of the trifurcation graft is sutured to the aorta around the celiac axis, superior mesenteric artery and right renal artery. The left renal artery is anastomosed to the second limb of the trifurcation graft

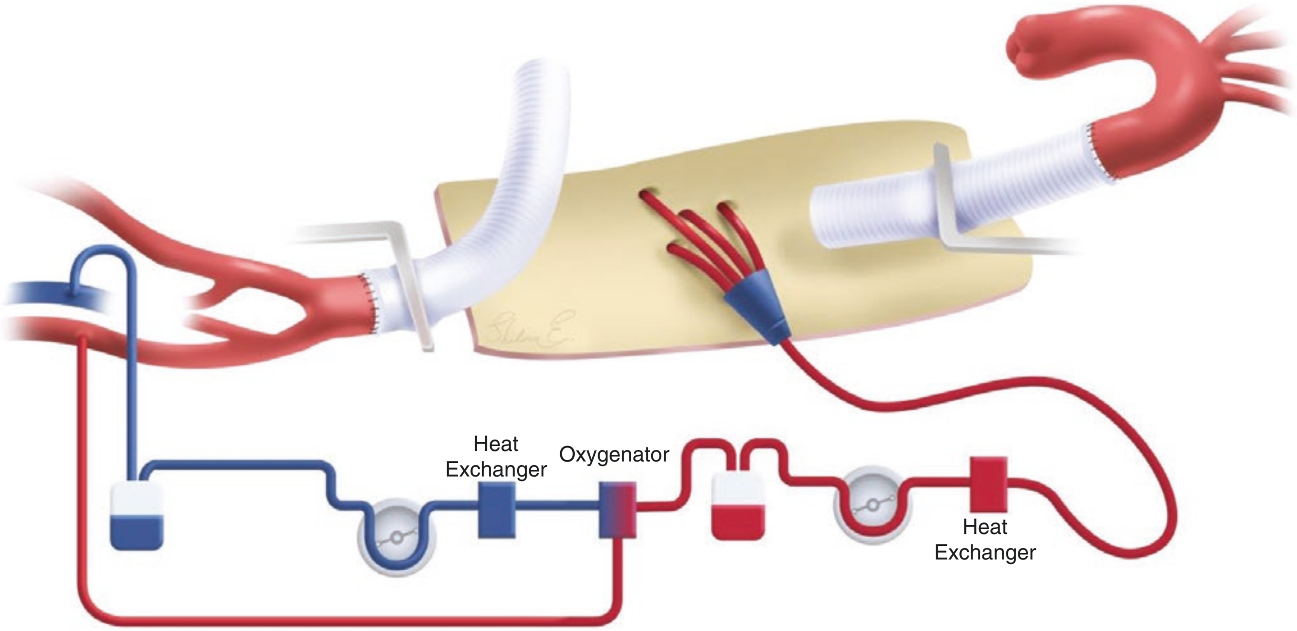

Fig. 56.13 Note the position of the clamps on the graft. The celiac axis, superior mesenteric artery and renal arteries are directly perfused from the circuit

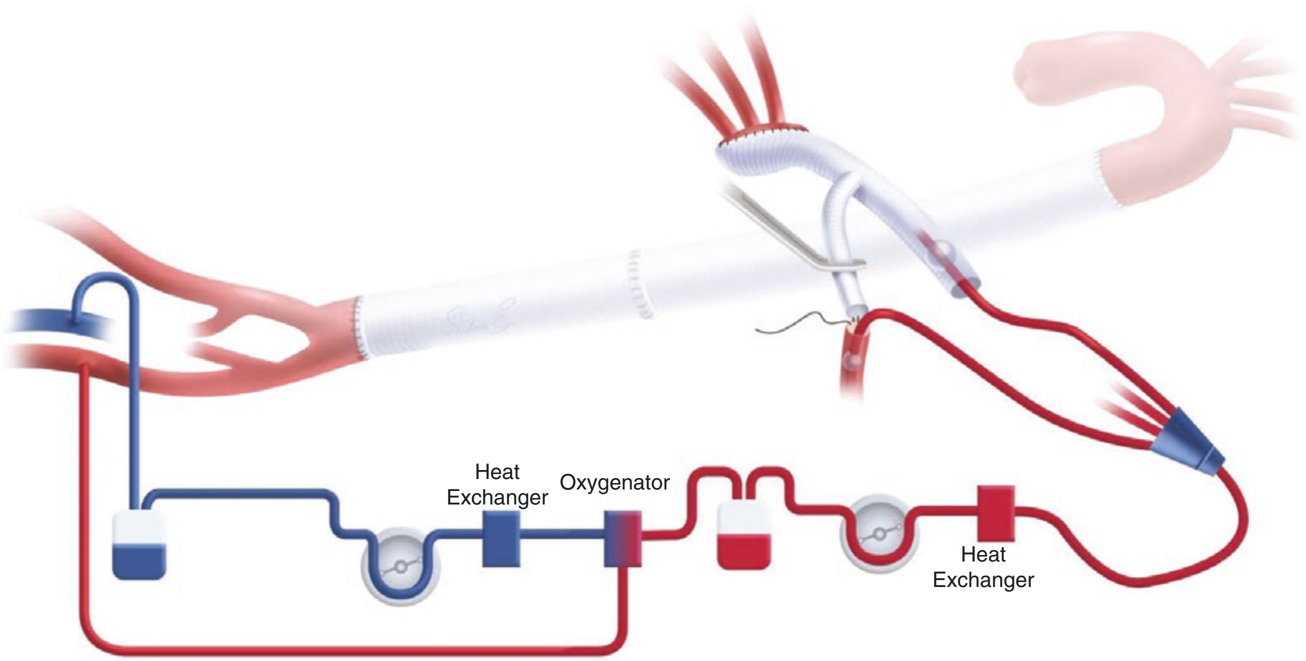

Fig. 56.15 The proximal and distal portions of the graft are connected to the perfusion circuit. The celiac axis, superior mesenteric artery and right renal artery are perfused via the main limb of the trifurcation graft. The left renal artery is directly perfused during construction of the anastomosis

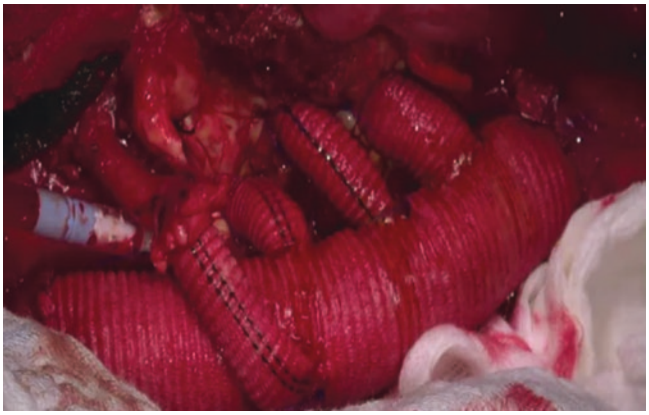

Fig. 56.16 The celiac axis, superior mesenteric artery and right and left renal arteries are individually anastomosed to the main graft

Usually, a separate 6 or 8 mm interposition graft is used to bypass the left renal artery.

For patients with extent IV TAAAs, we do not use distal aortic perfusion unless the patient had a previous descending thoracic aorta replacement with sacrifice of the intercostal arteries. In these cases, after the aorta is cross-clamped above the celiac axis, the aorta is opened longitudinally to the level of the aortic bifurcation and the left renal artery is detached. If CPB is used, the visceral and renal arteries are perfused with blood using balloon-tipped catheters at a rate of 200–300 cc/min. The distal anastomosis is performed first between the graft and aortic bifurcation to allow for distal aortic perfusion followed by the proximal anastomosis between the beveled graft and a segment of the aorta containing the visceral and right renal arteries. The left renal artery is next reattached with a 6 or 8 mm interposition graft.

However in most cases, the proximal anastomosis between the visceral and right renal arteries and the graft will be done first as previously described. Subsequently, the clamp will be moved distal to the anastomosis allowing perfusion of the visceral and renal arteries. The left renal artery will be then reattached with a separate 6 or 8 mm interposition graft. Lastly, the distal anastomosis will be performed between the graft and the aortic bifurcation.

For DTAA, after proximal and distal control has been achieved, the aorta is opened and the proximal and distal anastomoses will be performed as previously described. In extensive DTAA, reimplantation of distal thoracic intercostal arteries may be necessary using the island technique.

Outcomes After Open Repair of DTAA and TAAA

We performed open repair in 250 patients with DTAA and TAAA from 2000 to 2017. DTAA was found in 33% and TAAA in 67% of total patients. As shown in Fig. 56.18, medial degeneration was the most common etiology followed by chronic dissection and atherosclerosis. Figure 56.19 illustrates the aneurysm extent repaired. Extent I TAAA was most frequently observed. Figure 56.20 shows that these repairs were elective in the vast majority of cases (73%).

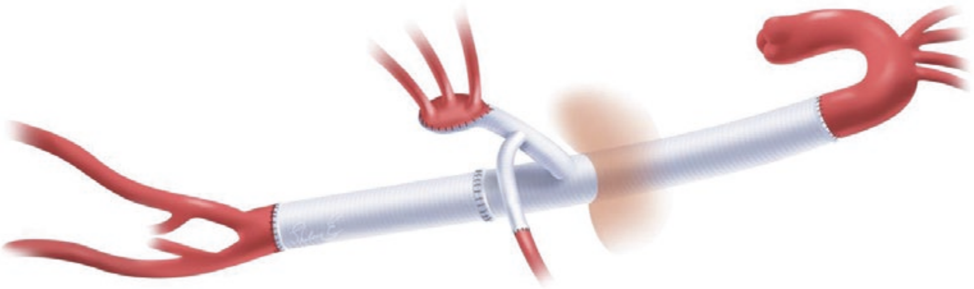

Fig. 56.17 Extent II thoracoabdominal aortic aneurysm repair

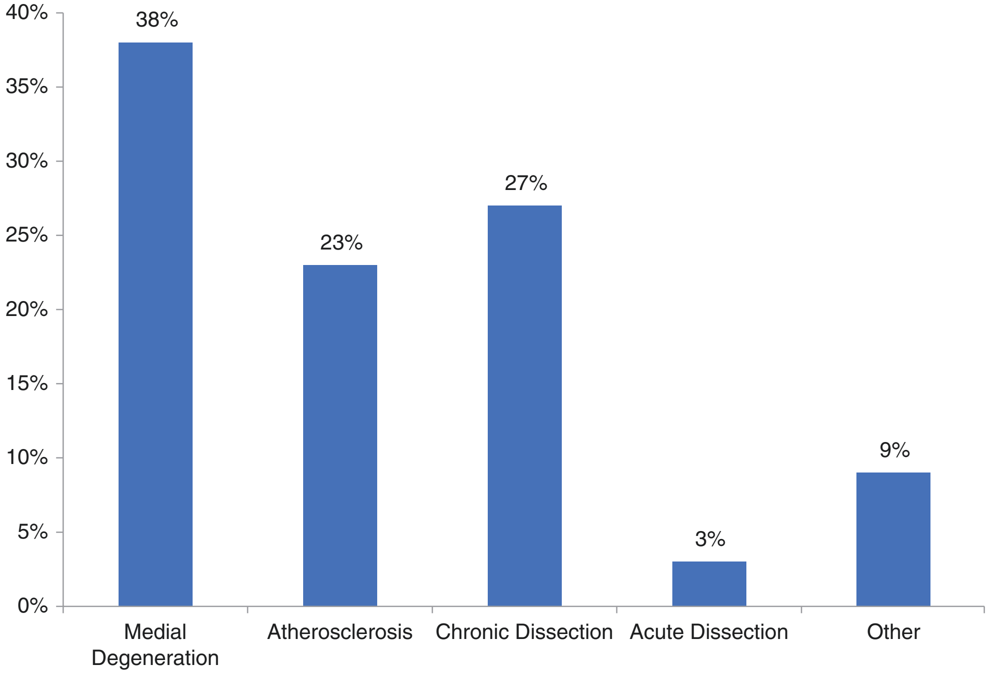

Fig. 56.18 Etiologies of descending thoracic aortic aneurysms and thoracoabdominal aortic aneurysms in our series

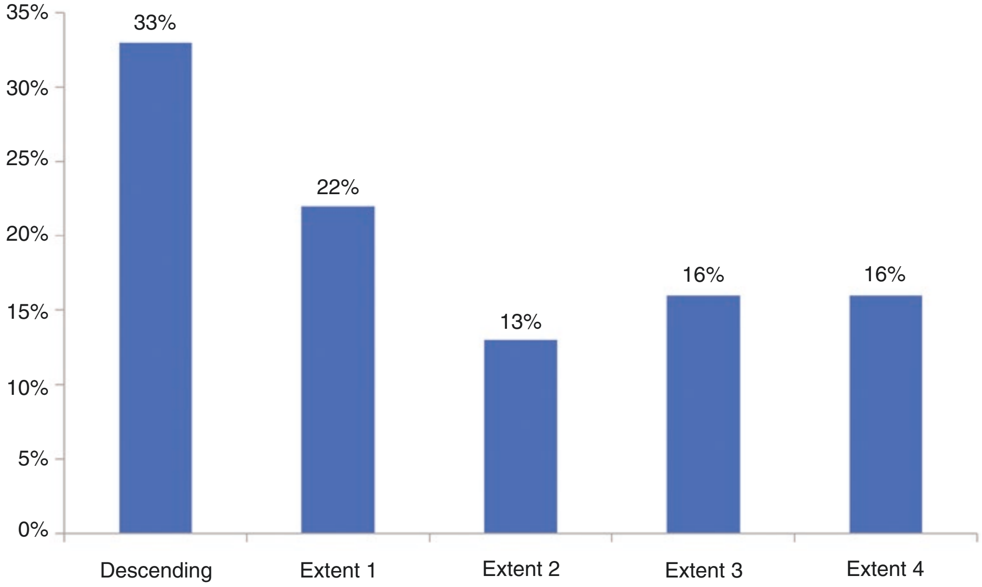

Fig. 56.19 Distribution of aortic aneurysms in our series

Distal perfusion, operative variables, mortality and morbidity and operative complications are shown in Table 56.4. Mortality was 2.4% and 10.2% for DTAA and TAAA, respectively. Paraplegia was 1.2% and 1.8% for DTAA and TAAA, respectively.

Figure 56.21 illustrates Kaplan-Meier survival analysis in the presence and absence of dissection. At 1 year, survival was 95% and 80% in the presence and absence of dissection;

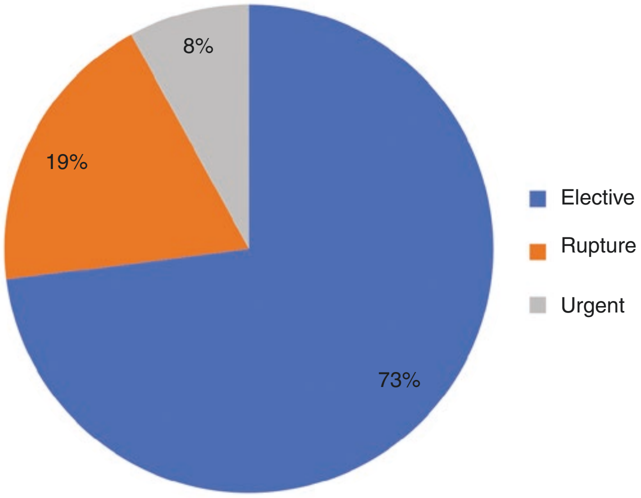

Fig. 56.20 Mode of presentation in our series

Table 56.4 Distal perfusion, operative variables, mortality and morbidity and operative complications in our series

	DTAA (n = 83)	TAAA (n = 167)	Overall (n = 250)
Age	59 ± 15	64 ± 11	63 ± 12
Males	55 (66.2)	103 (61.7)	158 (63.2)
Distal perfusion			
No distal perfusion	10 (12)	47 (28.1)	57(22.8)
Femoral-femoral	38 (45.8)	80 (48)	118(47.2)
Atrial-femoral	35 (42.2)	40 (23.9)	75(30)
DHCA	24 (28.9)	46 (27.5)	70(28)
Operative variables			
Aortic X time	39 ± 15	56 ± 21	51 ± 21
CPB time	99 ± 84	109 ± 89	105 ± 87
DHCA time	29 ± 6	28 ± 10	28 ± 8
Mortality and morbidity			
Mortality	2 (2.4)	17 (10.2)	19(7.6)
Paraplegia	1 (1.2)	3 (1.8)	4(1.6)
Operative complications			
Post-operative bleeding	4 (4.8)	5 (3)	9(3.6)
Stroke	3 (3.6)	5 (3)	8(3.2)
New onset renal complications			
New onset renal insufficiency (Cr > 2.5)	6 (7.2)	17 (10.2)	23(9.2)
New onset hemodialysis	4 (4.8)	3 (1.8)	7(2.8)
Ventilation >48 h	19 (22.9)	73 (43.7)	92(36.8)

CPB cardiopulmonary bypass, *Cr* creatinine, *DHCA* deep hypothermic circulatory arrest, *DTAA* descending thoracic aortic aneurysms, *TAAA* thoracoabdominal aortic aneurysms

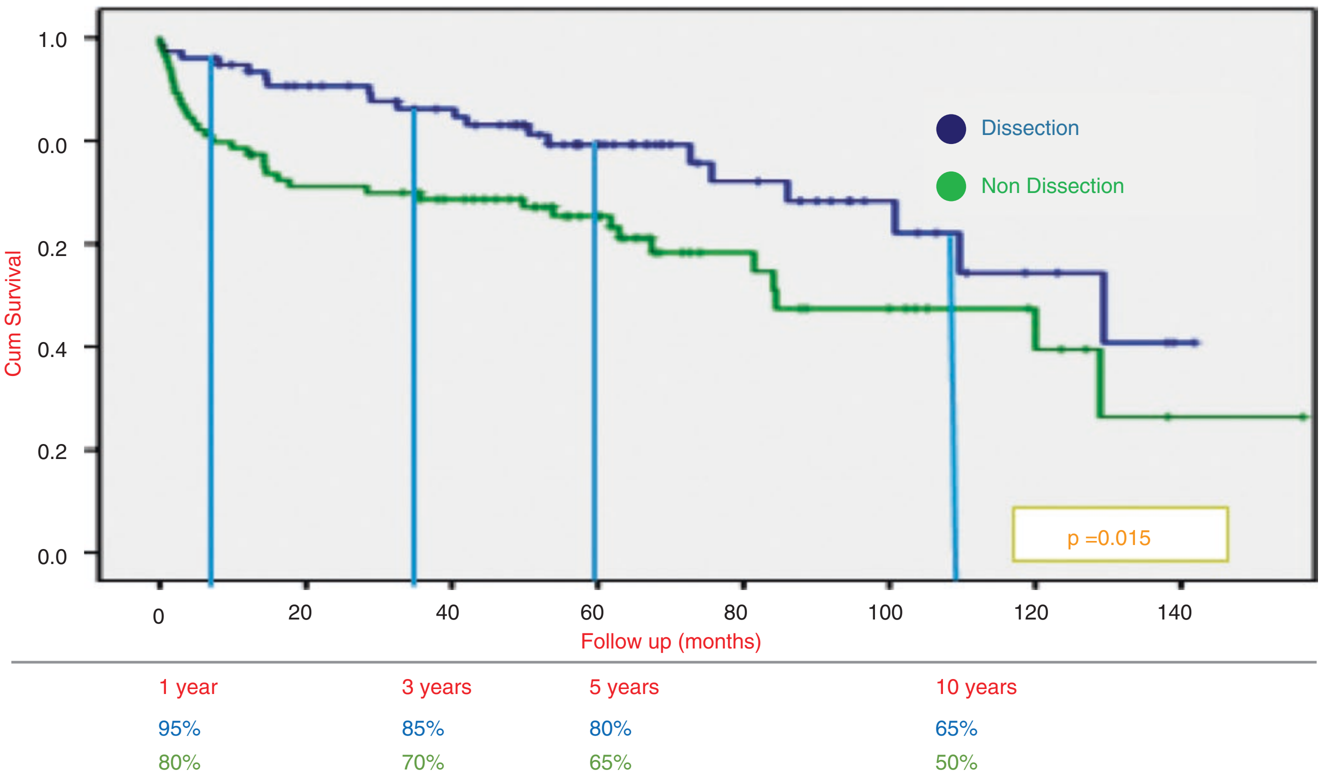

Fig. 56.21 Kaplan-Meier survival analysis in the presence and absence of dissection for descending thoracic aortic aneurysms and thoracoabdominal aortic aneurysms in our series

at 5 years 80% and 65%, respectively and at 10 years 65% and 50%, respectively. Our data are comparable to results obtained from other series [4, 12–14].

Conclusions

DTAA and TAAA are lethal diseases that often require urgent attention. Aneurysm size is the most accepted factor in establishing the timing of elective repair. CT scan and MRI are most commonly used diagnostic tools. Open repair still remains the gold standard treatment. Distal aortic perfusion, cerebrospinal fluid drainage, and selective visceral and renal artery perfusion are important adjuncts in preventing paraplegia and end-organ ischemia. Deep hypothermic circulatory arrest is an important technique when proximal clamping is not feasible. Acceptable rates of mortality, paraplegia, stroke, and renal insufficiency can be achieved using these specialized techniques.

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Aortic Arch Aneurysms

57

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High Yield Facts

- Isolated aortic arch aneurysms are rare.
- Most arch aneurysms occur as an extension of an ascending or descending thoracic aortic aneurysm.
- Most thoracic aortic aneurysms are asymptomatic and are discovered incidentally, or when catastrophic complications such as rupture or dissection occur.
- The growth rate of an arch aneurysm is between 0.07 and 0.2 cm/year.
- Surgery for an asymptomatic isolated arch aneurysm is indicated at a size of ≧5.5 cm.
- The main imaging modalities used for diagnosing pathology of the aortic arch are computed tomography and magnetic resonance imaging.
- Total open arch replacement is the gold standard approach for aortic arch repair and deep hypothermic circulatory arrest (DHCA) is a safe and effective method for intra-operative cerebral protection.

Introduction

According to the Center for Disease Control and Prevention, aortic aneurysms were the 15th leading cause of death in 2007 in individuals above the age of 65 years [1]. Aortic aneurysm is defined as a permanent, localized dilation that is at least 50% greater than the normal diameter at that anatomic level. Aortic aneurysms can occur anywhere along the aorta [2].

Isolated aortic arch aneurysms are a ‘rare bird’ as most aortic arch aneurysms occur as an extension of the adjacent ascending or descending thoracic aorta [2]. A study conducted on 780 patients with thoracic aortic aneurysms, identified only six with isolated arch aneurysms. Arch aneurysms may be fusiform or saccular (Fig. 57.1), with neither morphology influencing the risk of expansion or rupture. However, the higher blood pressure and shear stress at the arch are thought to increase the risk of rupture for aneurysms at this point [3]. Aortic arch aneurysms almost always begin as a penetrating aortic ulcer on the undersurface of the arch and develop into a saccular aneurysm.

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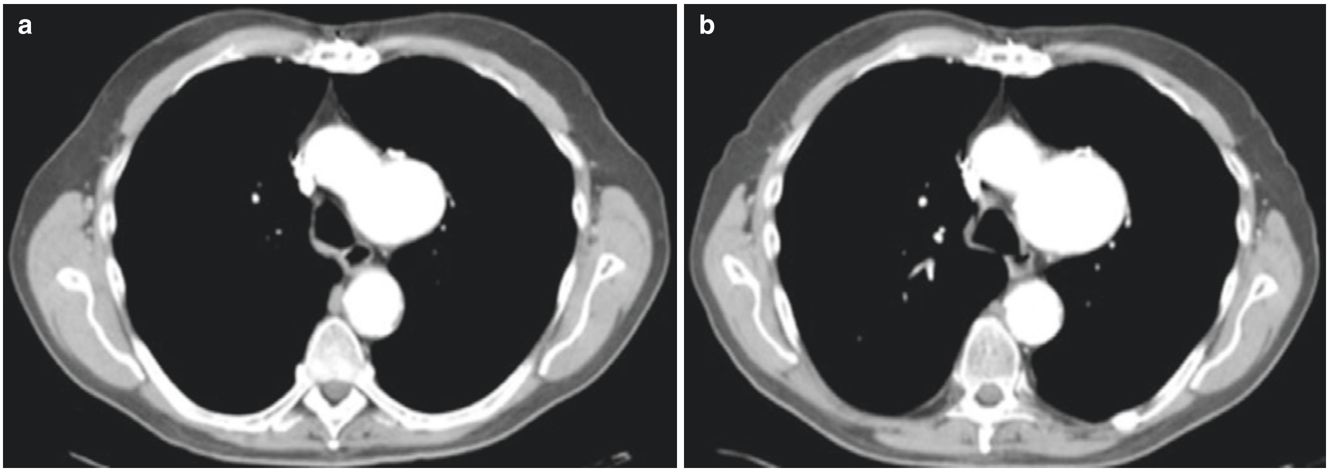


Fig. 57.1 Computed tomography scan. (**a**) Saccular arch aneurysm. (**b**) Follow up 2 years later showing saccular arch aneurysm which has increased in size

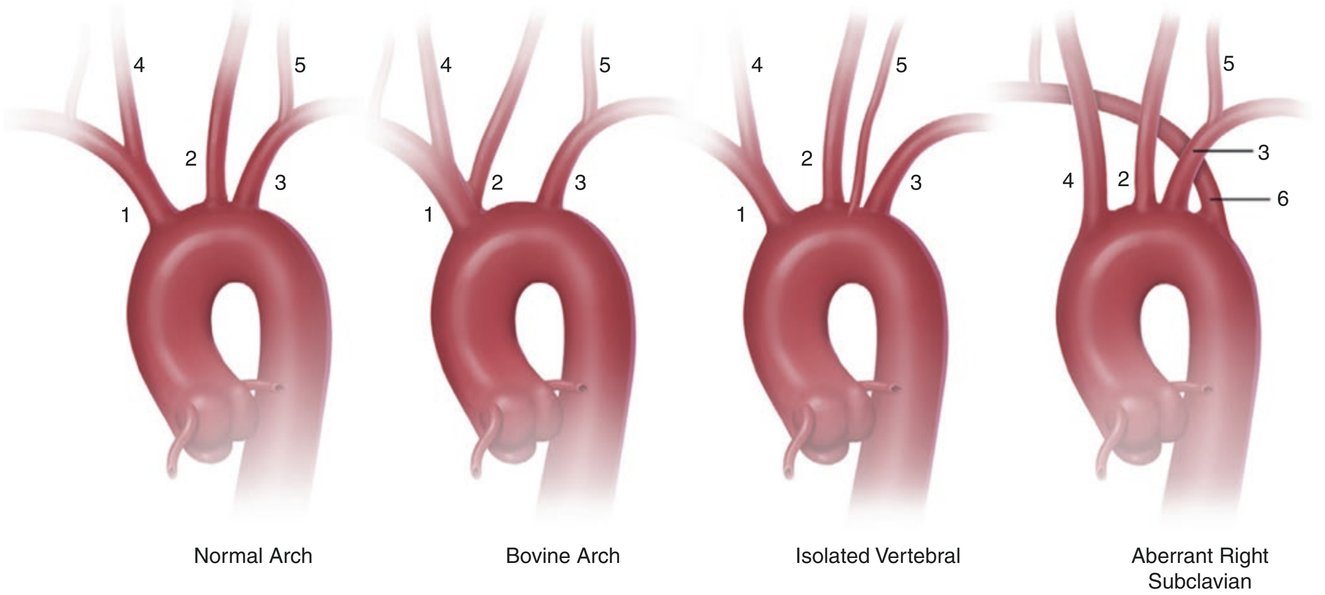


Fig. 57.2 Aortic arch branching patterns. 1 = Brachiocephalic artery; 2 = Left common carotid artery; 3 = Left subclavian artery; 4 = Right common carotid artery; 5 = Left vertebral artery; 6 = Aberrant right subclavian artery. (Reprinted with permission from Dumfarth J, Chou AS, Ziganshin BA, et al. Atypical aortic arch branching variants: A novel marker for thoracic aortic disease. J Thorac Cardiovasc Surg 2015;149(6):1586–1592 [9])

Anatomy

The aortic arch begins proximal to the origin of the brachiocephalic artery, continues superiorly and posteriorly, and terminates on the lateral aspect of the vertebral column. The arch gives off three branches along its course: the brachiocephalic, left common carotid, and left subclavian arteries [4]. Several variations in aortic arch branch patterns are seen in the general population. These branch pattern variants include:

- Common origin of the left common carotid artery and brachiocephalic artery (bovine aortic arch) (prevalence varies from 1% to 27.4% amongst various studies) [5].
- Left vertebral artery arising directly from the aorta (prevalence of 5–6%) [6].
- Left sided aortic arch with an aberrant right subclavian artery (prevalence of 0.5–2%) [7].
- Aberrant left subclavian artery [8].
- Right sided aortic arch [8].

Some branch variants show a stronger association with thoracic aortic disease. Prior work by our group has shown a higher prevalence of bovine aortic arch, isolated left vertebral artery and aberrant right subclavian artery in patients with diseases of the thoracic aorta (Fig. 57.2) [9]. Bovine arches, in particular, are more commonly associated with thoracic aortic pathology. These patients also appear to be slightly younger, with an average age at presentation being 56.7 years as compared to 60.1 years for thoracic aneurysm patients without arch anomalies [9].

Aortic Arch Pathology

Thoracic aortic aneurysm, although a virulent disease, is an indolent process with a yearly growth rate of 0.12 cm (Fig. 57.3). The descending thoracic aorta grows at a faster rate (0.3 cm/year) compared to the ascending aorta (0.1 cm/year) [10]. Studies have shown the growth rate of the aortic arch to be 0.07–0.2 cm/year [11]. The initial size of the aneurysm influences its growth rate, with larger aneurysms growing faster than smaller ones. A positive family history, older age, female sex, hypertension, chronic obstructive pulmonary disease, and an aortic dissection are all risk factors for faster aortic growth [11].

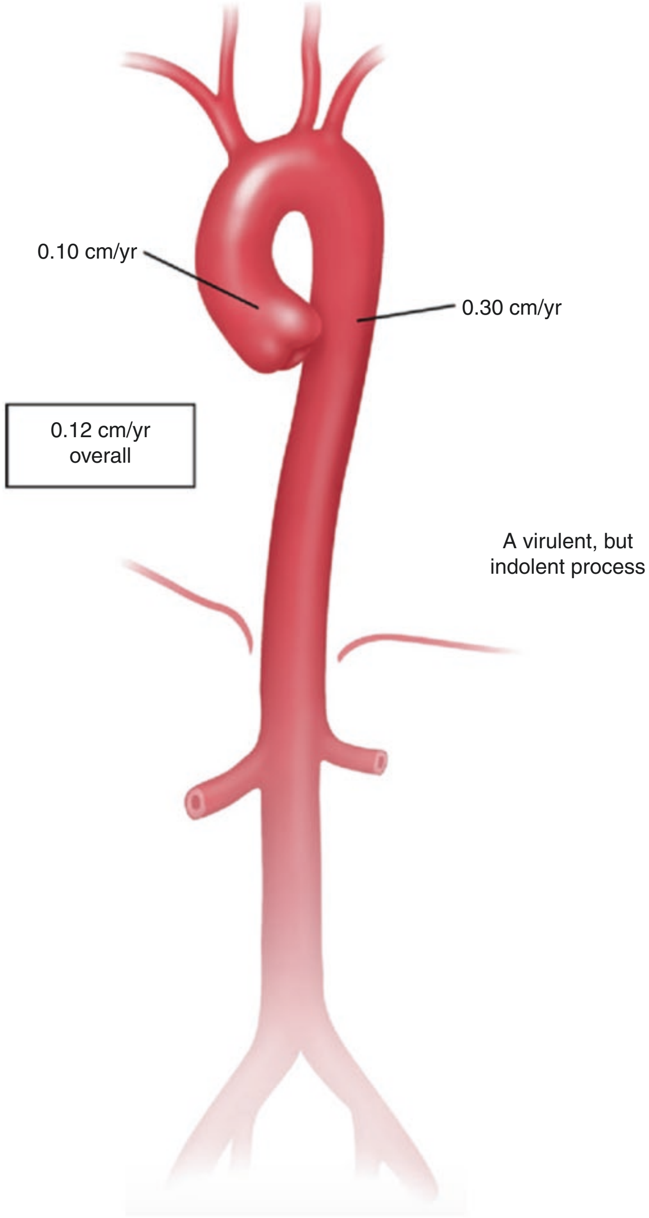


Fig. 57.3 Growth rate of aneurysmal thoracic aorta. (Reprinted with permission from Elefteriades JA, Farkas EA. Thoracic aortic aneurysm clinically pertinent controversies and uncertainties. J Am Coll Cardiol 2010;55(9):841–857 [3])

Histologically, aortic aneurysms are characterized by medial degeneration resulting from a loss of elastic fibers and increased deposition of proteoglycans. Matrix metalloproteinases, particularly MMP-2 and MMP-9, have been implicated in multiple studies and are known to have elastolytic activity [12, 13].

Other pathologic processes involving the arch can be grouped into *acute aortic syndrome* which comprises acute aortic dissection, intramural hematoma and penetrating aortic ulcer. All arch pathologies can present a challenge to surgical and endovascular treatment since patients are often asymptomatic until they present with a catastrophic life-threatening event [14].

Clinical Presentation

Most aneurysms are asymptomatic and discovered incidentally on imaging. Symptoms may result from chronic compression of a nearby structure or from dissection, resulting in excruciating acute pain. Aortic arch aneurysms may cause hoarseness, dysphagia, respiratory symptoms, upper body edema, and dull, aching pain due to compression of the left recurrent laryngeal nerve, esophagus, airway, superior vena cava and chest wall, respectively [2]. The patient may present with a thromboembolic event or aortic regurgitation. Rupture of an arch aneurysm can result in bleeding into the pleural cavity, mediastinum, esophagus and tracheobronchial tree, and dissection of the arch can cause cerebral malperfusion [2].

Prior work by our group has identified certain clinical correlates and detectable manifestations of thoracic aortic aneurysms, which should prompt screening for aneurysmal disease in such patients. These conditions include abdominal aortic aneurysm (AAA), intracranial aneurysm, bicuspid aortic valve, coarctation of the aorta, bovine aortic arch, origin of left vertebral artery directly from aortic arch, polycystic kidney disease, intra-abdominal simple cysts (kidney), temporal arteritis, and autoimmune syndromes (Behcet's, Reiter's, ankylosing spondylitis, early onset osteoarthritis) (Fig. 57.4) [15].

Imaging

A variety of factors influence the diameter of the "normal aorta": patient age, sex, and body size, as well the point of aortic measurement and the imaging technique used [12].

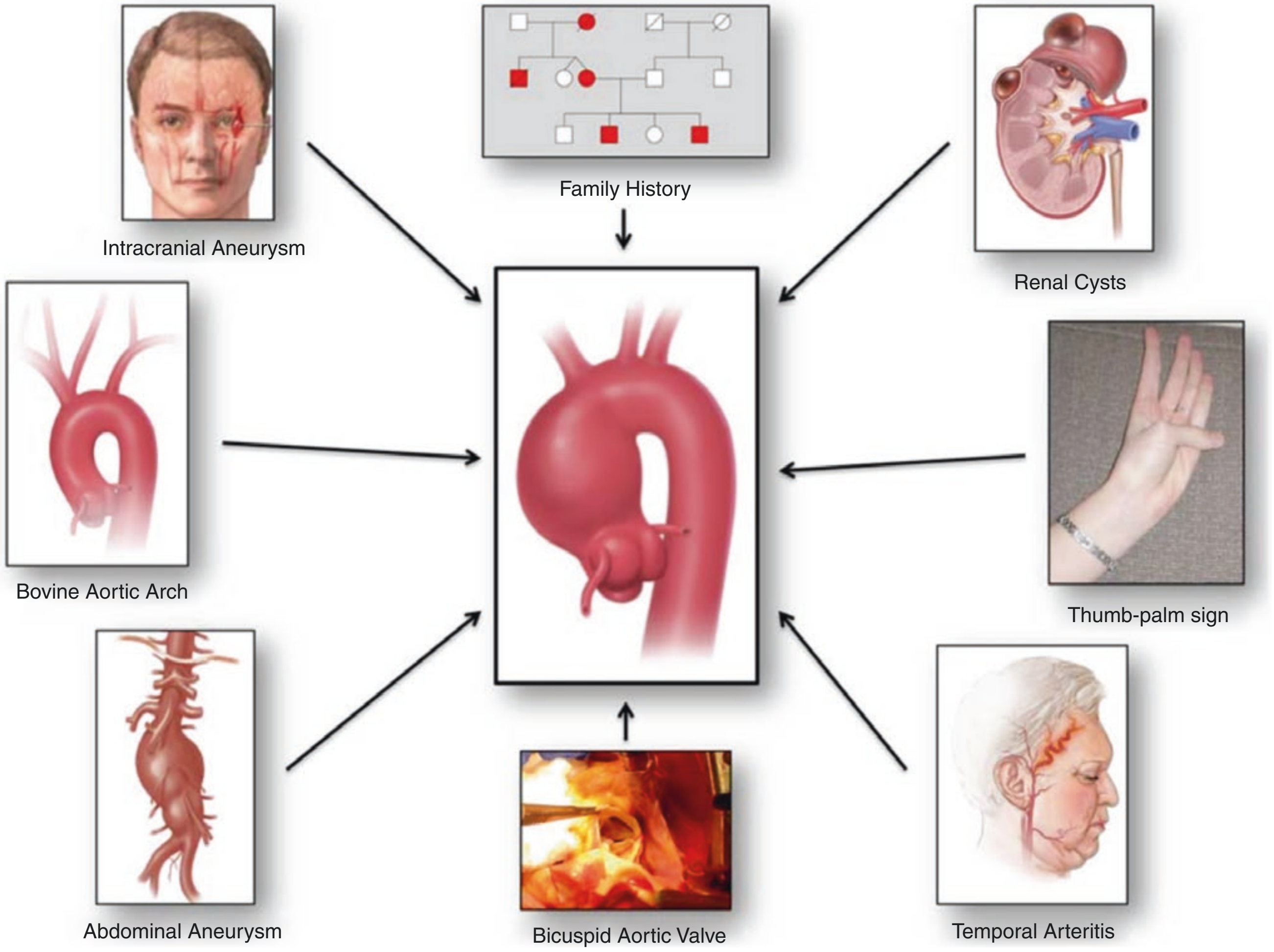


Fig. 57.4 Paradigm of "Guilt by Association" for detection of silent thoracic aortic aneurysms. (Reproduced with permission from Elefteriades JA, Sang A, Kuzmik G, et al. Guilt by association: paradigm for detecting a silent killer (thoracic aortic aneurysm). Open Heart 2015;2: e000169 [15])

It is important to correctly measure the size of the aorta as this influence's management. Transthoracic and transesophageal echocardiography can visualize the aortic valve and several centimeters of the proximal ascending aorta, but they are not generally useful modalities for the aortic arch due to acoustic shadowing from the trachea. A dilated aorta may be appreciated on a chest radiograph, but a simple X-ray cannot be used to conclusively determine the presence of aortic pathology. A widened mediastinum is suggestive of aortic dissection and an enlarged aortic knob may indicate the presence of an arch aneurysm (Figs. 57.5 and 57.6) [16].

Computed tomography (CT) and magnetic resonance imaging (MRI) can visualize the entire aorta and the surrounding structures. Axial, sagittal and coronal images from CT and MRI can provide meaningful measurements. However, axial images through the arch produce an oblong instead of a circular contour, giving an inaccurate aortic diameter when measured along the long axis [2, 10].

Figure 57.7 illustrates the complexity of measuring an arch aneurysm on a CT scan and the importance of using a multiplanar approach to visualize arch pathologies.

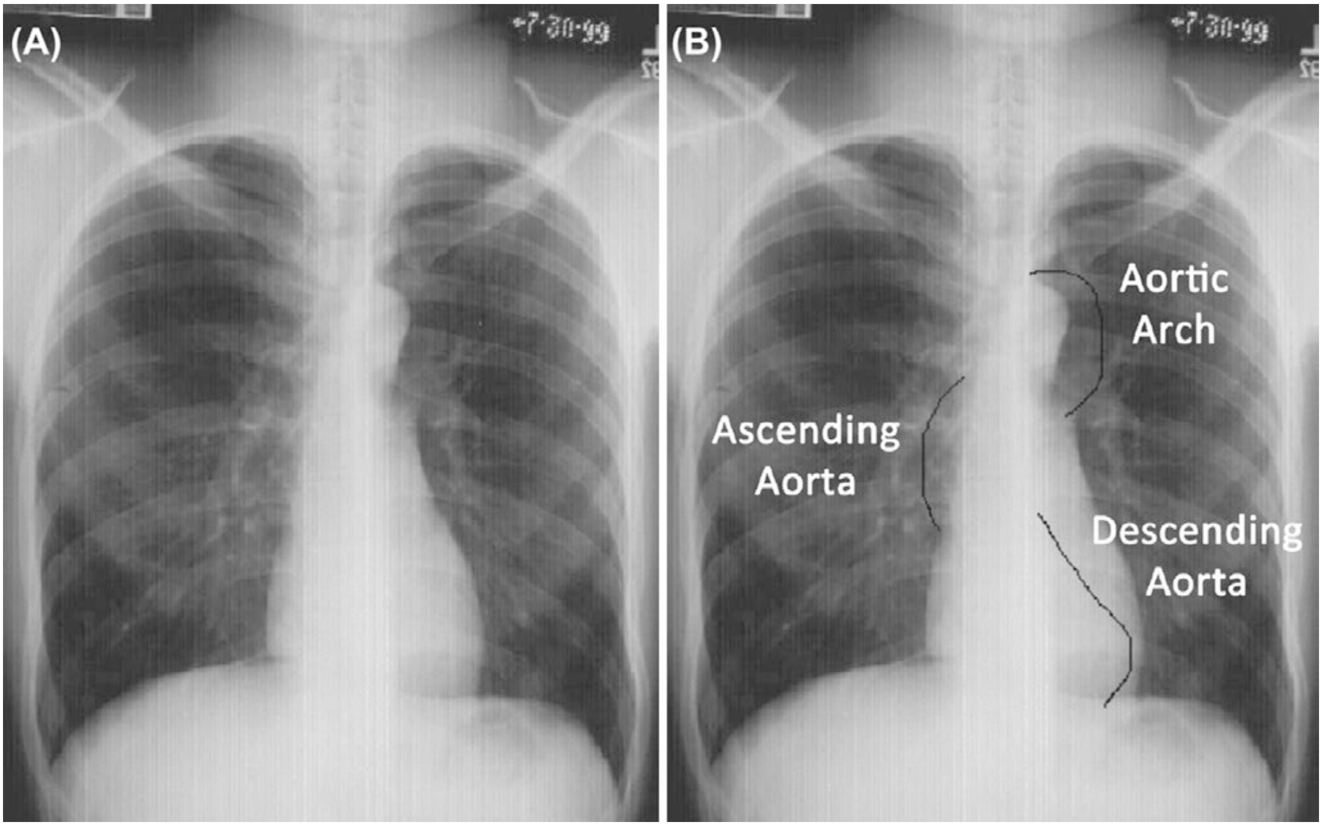


Fig. 57.5 (**a**) Normal chest. X-ray (**b**) Same chest X-ray with areas where ascending, arch and descending aneurysm shadows may appear. (Reproduced with permission from Danias P. Imaging of aneurysms and dissections: chest x-ray, echo, computed tomography, magnetic resonance imaging In: Elefteriades JA, editor. Acute Aortic Disease. 1 ed.: TAYLOR & FRANCIS GROUP LLC; 2007. p. 39–66 [16].)

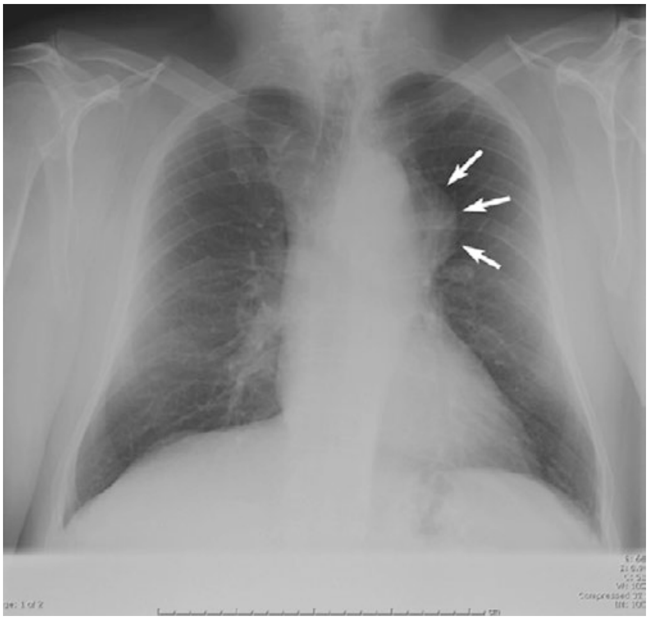


Fig. 57.6 Aortic arch aneurysm on chest X-ray. (Reproduced with permission from Danias P. Imaging of aneurysms and dissections: chest x-ray, echo, computed tomography, magnetic resonance imaging In: Elefteriades JA, editor. Acute Aortic Disease. 1 ed.: TAYLOR & FRANCIS GROUP LLC; 2007. p. 39–66 [16])

Treatment

Criteria for Surgical Intervention

Surgical intervention for an aortic arch aneurysm poses several unique challenges due to the risks associated with cerebral protection and the higher mortality and stroke rate seen with arch replacement [17].

Several 'hinge points' have been identified, in thoracic aortic size, at which the risk for dissection or rupture significantly increases. For the ascending aorta, a sharp increase is seen between 5.25 and 5.5 cm and then again between 5.75 and 6 cm (Fig. 57.8) [18]. For the descending aorta the hinge point is seen at 7 cm (Fig. 57.9) [19]. The current guidelines recommend surgery for asymptomatic ascending and isolated arch aneurysms at 5.5 cm, and asymptomatic descending aortic aneurysms at a size of 6.5 cm [12]. The aortic arch lies between these two zones (ascending and descending). As isolated arch aneurysms are rare, surgical decision making is usually based on the size of the aortic arch as well as the contiguous involved ascending or descending segment. However, recent data suggest that a left-ward shift towards smaller aortic sizes may be warranted [20]. Since patients

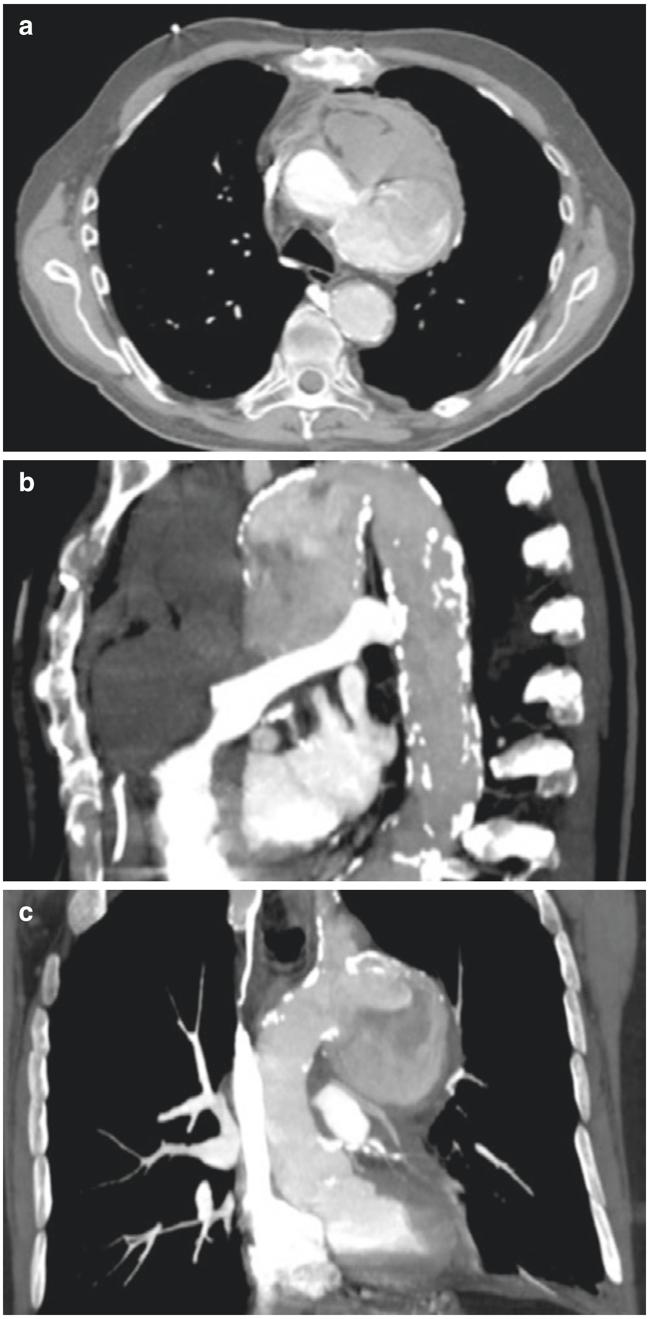


Fig. 57.7 Computed tomography scan showing ruptured saccular arch aneurysm. (**a**) Axial view. (**b**) Sagittal view. (**c**) Coronal view

with Marfan syndrome, Loeys-Dietz, Ehlers-Danlos and other genetically mediated aortopathies are prone to dissection at smaller sizes, surgical intervention is carried out between 4.0 and 5.0 cm (Fig. 57.10) in case of those diseases (or related genetic conditions) [21–23]. The majority of arch aneurysms have an adjacent aneurysm of the ascending or descending aorta, therefore prophylactic surgery should be performed once the above size criteria are met or if the patient is symptomatic, irrespective of size [17, 24].

Perfusion and Cerebral Protection

Aneurysms involving the thoracic aortic arch can be managed by several different surgical approaches, all necessitating cerebral protection during branch vessel occlusion and revascularization [2]. This can be achieved by hypothermic circulatory arrest. Circulatory arrest creates a bloodless field for the surgeon to operate. Hypothermia produces an exponential decrease in metabolic rate, with a drop of about 50% per 6 °C decrease in body temperature [25]. Studies have shown that the metabolic rate of the human body falls to 12–25% of the normal metabolic rate at a temperature of 18 °C (Fig. 57.11) [26].

While hypothermia is a key ingredient, three main techniques are available for cerebral protection during deep hypothermic arrest in aortic arch replacement: (1) retrograde cerebral perfusion (RCP), (2) antegrade cerebral perfusion (ACP), and (3) straight deep hypothermic circulatory arrest (DHCA) [27]. These are compared in Table 57.1 [28].

Deep Hypothermic Circulatory Arrest (DHCA)

Straight DHCA has been the preferred method for the vast majority of complex procedures involving the aortic arch done at our institution [29]. Our group studied 613 patients who underwent aortic surgery. Of these 77.3% had hemiarch replacement and 20.4% had total arch replacement, 85 of whom underwent a conventional two-stage elephant trunk procedure (discussed in the subsequent section). The mean DHCA time was 29.7 ± 8.5 min (range, 10–62 min) with a majority having a duration of less than 40 min [31].

The procedures are performed via a median sternotomy on cardiopulmonary bypass. Patients are cooled slowly, over 30–35 min, to a bladder temperature of 20 °C (for hemiarch replacement) or 18 °C (for arch replacement). The patient's head is topically cooled with ice, before and during DHCA. In order to minimize the DHCA time, the distal arch anastomosis is often done proximal to the left subclavian artery, with a 2- (or 3-) vessel patch reimplantation of the head vessels (Fig. 57.12) [30]. Patients were gradually rewarmed before being weaned from cardiopulmonary bypass [31].

Our experience showed an operative mortality (mortality within 30 days of surgery or during postoperative stay) of 2.9% for all cases and 1% for elective cases without aortic dissection. Postoperative stroke rate was 2%, with higher stroke rates (10.5%; $P = 0.05$), observed with DHCA time >50 min [31]. We believe DHCA to be a safe and effective means of cerebral protection during aortic arc surgery [31].

Fig. 57.8 Estimated probability of rupture or dissection of the ascending aorta by aneurysm size. (Reproduced with permission from Zafar MA, Li Y, Rizzo JA, et al. Height alone, rather than body surface area, suffices for risk estimation in ascending aortic aneurysm. J Thorac Cardiovasc Surg 2018;155(5):1938–1950 [18])

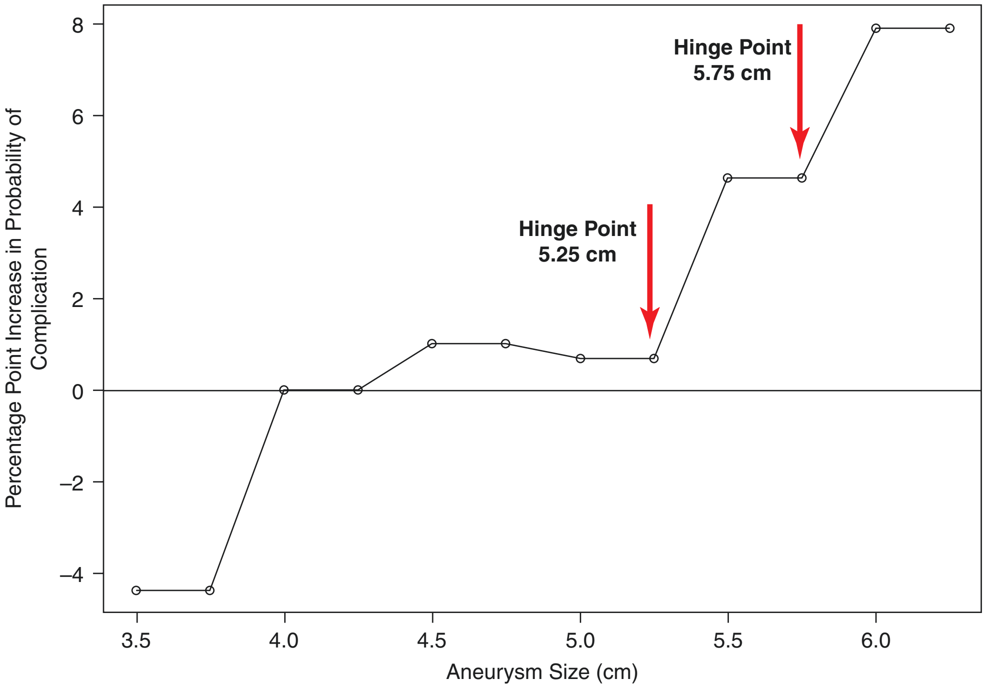
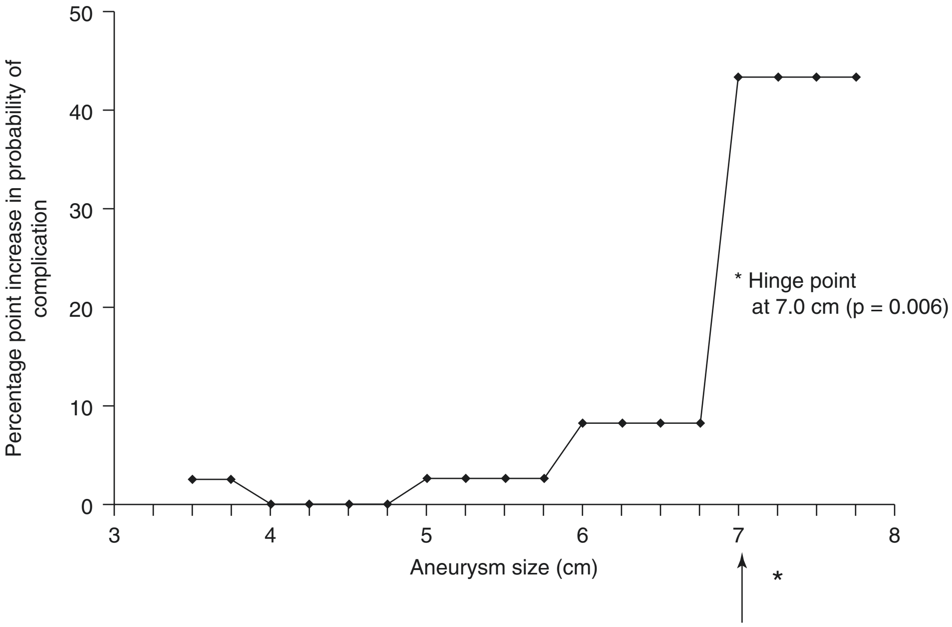


Fig. 57.9 Estimated effect of descending aortic aneurysm size on the risk of complication. (Reproduced with permission from Coady MA, Rizzo JA, Hammond GL, et al. What is the appropriate size criterion for resection of thoracic aortic aneurysms? *J Thorac Cardiovasc Surg.* 1997;113(3):476–491 [19])



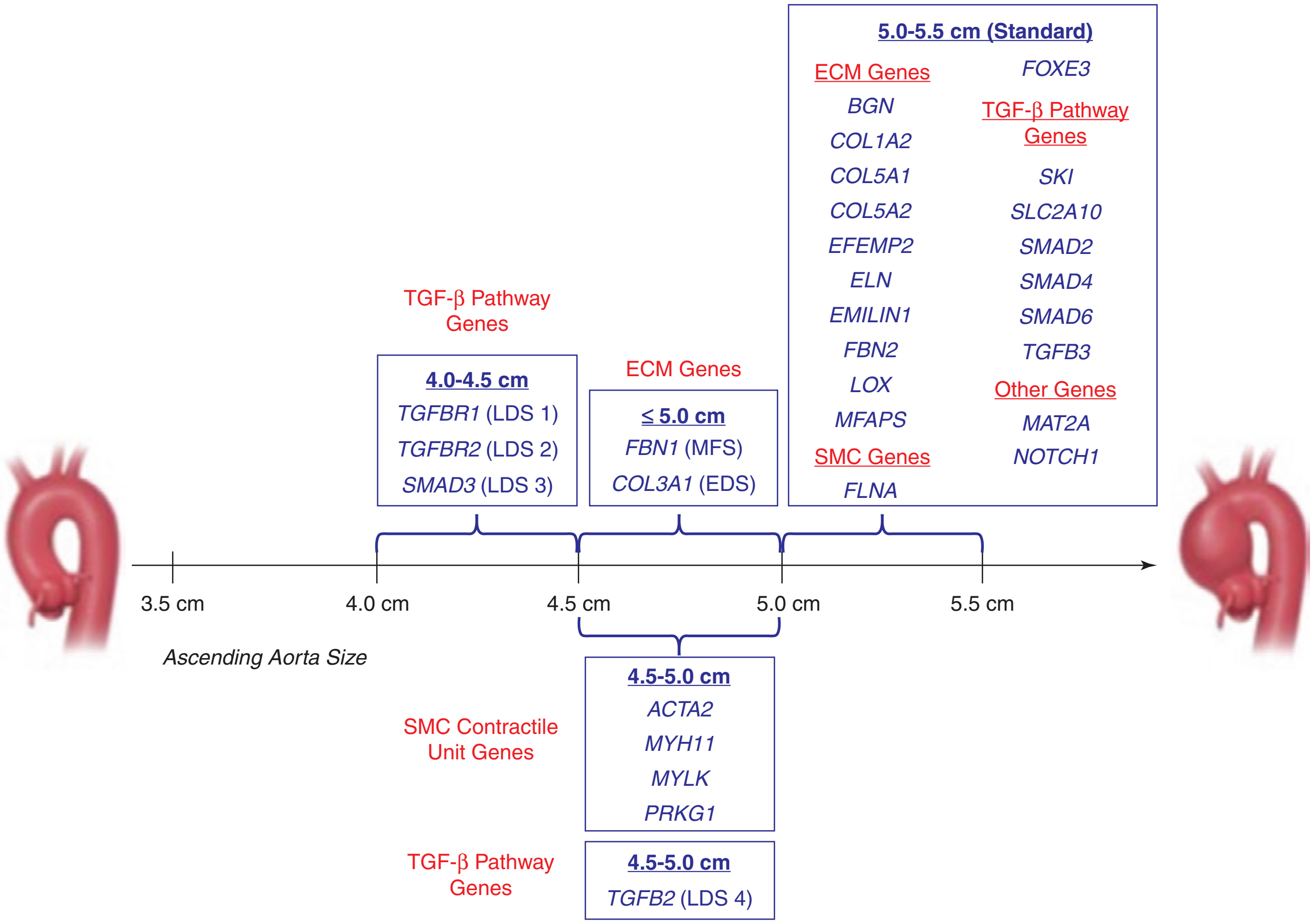

5.0-5.5 cm (Standard)
ECM Genes
BGN
COL1A2
COL5A1
COL5A2
EFEMP2
ELN
EMILIN1
FBN2
LOX
MFAPS
SMC Genes
FLNA
FOXE3
TGF-β Pathway Genes
SKI
SLC2A10
SMAD2
SMAD4
SMAD6
TGFB3
Other Genes
MAT2A
NOTCH1
TGF-β Pathway Genes
4.0-4.5 cm
TGFBR1 (LDS 1)
TGFBR2 (LDS 2)
SMAD3 (LDS 3)
ECM Genes
≤ 5.0 cm
FBN1 (MFS)
COL3A1 (EDS)
3.5 cm
4.0 cm
4.5 cm
5.0 cm
5.5 cm
Ascending Aorta Size
SMC Contractile Unit Genes
4.5-5.0 cm
ACTA2
MYH11
MYLK
PRKG1
TGF-β Pathway Genes
4.5-5.0 cm
TGFB2 (LDS 4)

Fig. 57.10 Simplified schematic illustration of ascending aorta dimensions for prophylactic surgical intervention divided by gene category: ECM genes, SMC contractile unit and metabolism genes, and TGF-β signaling pathway. *ECM* extracellular matrix, *LDS* Loeys-Dietz syndrome, *MFS* Marfan syndrome, *SMC* smooth muscle cell, *EDS* Ehlers-Danlos syndrome. (Reproduced with permission from Brownstein AJ, Ziganshin BA, Kuivaniemi H, Body SC, Bale AE, Elefteriades JA. Genes Associated with Thoracic Aortic Aneurysm and Dissection: An Update and Clinical Implications. Aorta (Stamford) 2017;5(1):11–20 [23])

Fig. 57.11 Drop in cerebral metabolic rate (to 12% of normothermic levels at 18 °C) with hypothermia. (Reprinted with permission from Kirklin JW, Barratt-Boyes BG. Cardiac surgery: morphology, diagnostic criteria, natural history, techniques, results, and indications. fourth ed. New York: Churchill Livingstone; 2013 [26])

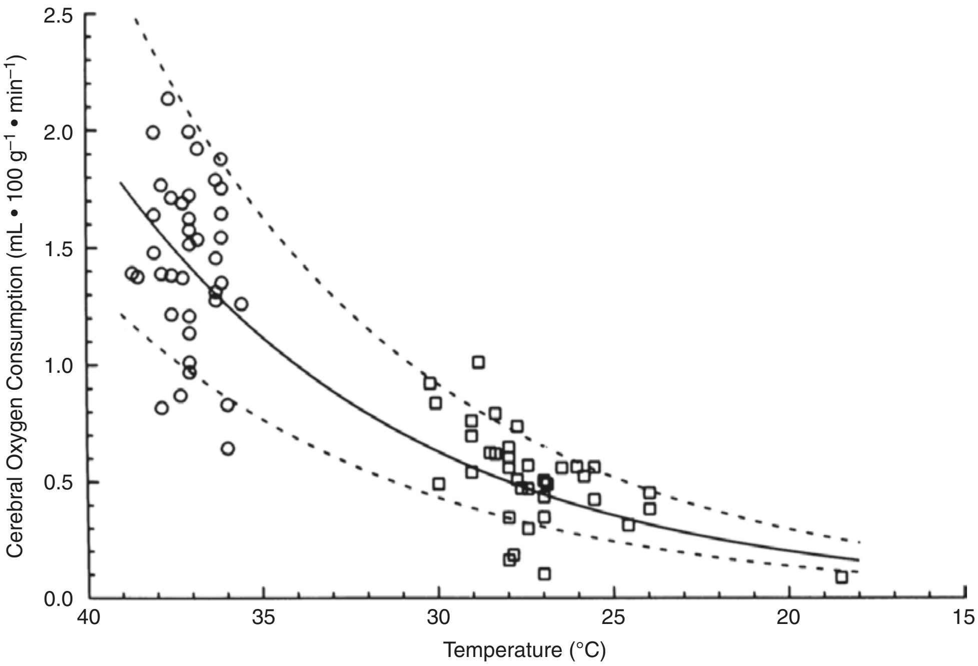


Table 57.1 Advantages and limitations of each cerebral protection strategy[a]

Technique	Advantage	Limitation	Comment
DHCA (Deep hypothermic circulatory arrest)	Safe for short periods of circulatory arrest Avoids cross-clamping of already diseased aorta	Concerns regarding safety of long periods of circulatory arrest. Increased incidence of permanent neurologic injury with >45 min of circulatory arrest. Conflicting data on transient effects with shorter (approximately 25 mins) ischemia	Generally used in more straightforward or acute cases
ACP (antegrade cerebral protection)	Permits longer periods of circulatory arrest than with straight DHCA	Requires the handling of sclerotic vessels; may result in the release of emboli	Technique most often used in the present era. Controversies regarding ideal site of cannulation for optimal perfusion
RCP (retrograde cerebral perfusion)	Flushes cerebral vasculature of toxic metabolic products and debris	Perfusion may be limited to the brain's surface, if any actually reaches brain tissue	Becoming less popular

[a] Reproduced with permission from Stein LH, Elefteriades JA. Protecting the brain during aortic surgery: an enduring debate with unanswered questions. J Cardiothorac Vasc Anesth 2010;24:316–21 [28]

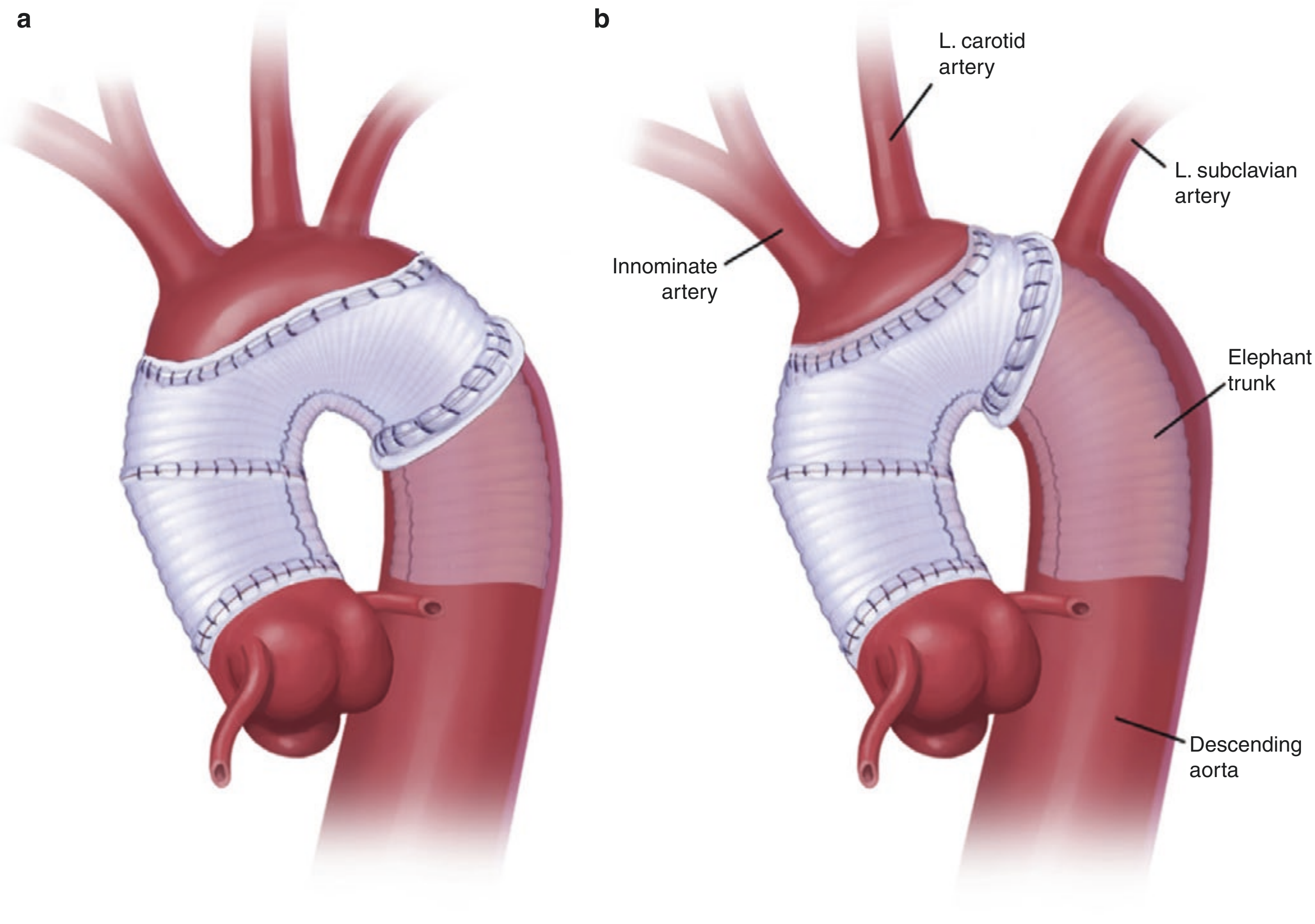


Fig. 57.12 Techniques for aortic arch replacement. (**a**) The 3-vessel Carrel patch technique. (**b**) The 2-vessel Carrel patch technique, preferred at our institution. (Reproduced with permission from Ziganshin BA, Rajbanshi BG, Tranquilli M, Fang H, Rizzo JA, Elefteriades JA. Straight deep hypothermic circulatory arrest for cerebral protection during aortic arch surgery: Safe and effective. J Thorac Cardiovasc Surg 2014;148(3):888–898 [30])

Retrograde Cerebral Perfusion (RCP)

Retrograde cerebral perfusion (15–24 °C) can be administered via the superior vena cava as an adjunct to the technique of profound hypothermia and circulatory arrest [32, 33].

The superior vena cava pressure should not exceed 25 mmHg, to prevent cerebraledema.

The largest positive experience with RCP comes from Safi and colleagues, who have reported data on 1193 patients. They found a mortality at 30 days of 9.3%; mortality was only 3% for those patients with a preoperative normal glomerular filtration rate [32, 33]. Many surgeons also feel that RCP is instrumental in flushing arteriosclerotic debris from the arch branches, thus protecting from stroke.

Anterograde Cerebral Perfusion (ACP)

Selective antegrade cerebral perfusion (usually performed via cannulation of the innominate and left common carotid arteries) aims to permit longer and safer circulatory arrest times by directly perfusing the brain with cold blood (12–16 °C) [28, 34]. The currently popular axillary perfusion technique for aortic surgery facilitates ACP, as the axillary cannula accomplishes the innominate artery perfusion without additional complexity [28]. ACP has shown a postoperative mortality rate between 11% and 16% [34–36]. The overall 5-year survival rate for true and dissecting aneurysm after aortic arch replacement in patients protected by selective cerebral perfusion was 59% and 63% respectively [37]. Renal failure, postoperative dialysis, and increased cerebral perfusion time are predictive of perioperative mortality, with age greater than 60 years representing a significant factor [35, 38].

Surgical Repair Techniques

The operative management for aneurysms that extend into the transverse aortic arch include hemiarch resection, total arch repair (TAR), Y-graft techniques, elephant trunk procedure, extensive single-stage repair, hybrid arch repair and hybrid elephant trunk repair. These are discussed in Table 57.2 and a comparison is made between the contemporary arch repairs based on the findings by Coselli et al. [2] (Table 57.3).

Total arch repair (TAR) remains the gold standard for aortic arch replacements [39]. In this procedure the entire aortic arch is replaced and a 'Carrel patch', which is an 'island' of aortic wall carrying the great vessels, is reattached to reestablish cerebral blood flow. Individual branch grafts to the head vessels can also be used [40]. Settepani and colleagues noted a mortality rate of 5.3% and permanent neurological deficit rate of 3.4% in the review of TAR outcomes [41].

Table 57.2 Options for surgical repair for aneurysms extending into the aortic arch[a]

1. Partial arch repairs (Hemi-arch)	• Include patch graft aortoplasty and hemiarch approaches • Do not directly involve the brachiocephalic vessels • Can be used for saccular aneurysms that originate from the lesser arch curvature and involve <50% of the aortic circumference • Arch vessels are left intact and the undersurface of the arch is replaced
2. Total arch repair	• Gold standard • Total replacement of the aortic arch • Reattachment of brachiocephalic vessels • Distal anastomosis at the descending thoracic aorta
3. Y-Graft techniques	• Trifurcated graft technique • Appears to improve outcomes by reducing embolization and minimizing cerebral ischemia • Includes single Y-graft approach, double Y-graft approach, elephant trunk approach with single Y-graft, elephant trunk approach with double Y-graft
4. Elephant trunk	• For extensive aneurysm involving the entire thoracic aorta • Repairs often involve two stages • Borst's elephant trunk procedure involves repairing proximal aorta first followed by distal repair • Advantages: easier dissection, shorter aortic clamping time, reduced injury to pulmonary artery and esophagus • Introduction of collared or "skirted" aortic arch graft has improved this approach
5. Extensive single-stage repair	• Single-stage repair for extensive disease involving the ascending, arch and descending thoracic aorta • Bilateral anterior thoracotomy performed with a transverse sternotomy (clamshell) incision (Kouchoukos) • Arch anastomosis done during a short period of hypothermic cerebral arrest
6. Hybrid arch repair	• Involves "debranching' some or all of the brachiocephalic arteries and using a stent graft to exclude the diseased aorta • Ishimura landing zones help indicate extent of hybrid arch repair • Done in specially designed hybrid operative suites that combine standard cardiothoracic operative equipment with specialty imaging device • Debranching procedure may be done off pump and without HCA
7. Hybrid elephant trunk repair	• Combines a standard open arch repair with an extended, distal endovascular repair • Can be done simultaneously or later • Less invasive than traditional elephant trunk and can be performed sooner • Frozen elephant trunk, is a modification of this approach

[a] Reproduced with permission from Coselli JS, Trocciola SM, de la Cruz KI, LeMaire SA. Arch Aneurysm. Mastery of Cardiothoracic Surgery. third ed.: Lippincott Williams & Wilkins; 2013 [2]

Table 57.3 Outcomes in contemporary aortic arch repair by operative approach[a]

Operative approach	Patients, n	Operative survival, n (%)	Stroke, n (%)	Renal failure, n (%)	Reoperation for bleeding, n (%)
Traditional partial arch replacement (hemi-arch)	165	155 (94)	7 (4)	4 (2)	9 (5)
Traditional total arch replacement	23	22 (96)	3 (13)	1 (4)	3 (13)
Y-graft technique	55	54 (98)	3 (5)	3 (5)	4 (7)
Total	243	231 (95)	13 (5)	8 (3)	16 (7)

Renal failure is defined as the need for dialysis at time of hospital discharge

[a] Reproduced with permission from Coselli JS, Trocciola SM, de la Cruz KI, LeMaire SA. Arch Aneurysm. Mastery of Cardiothoracic Surgery. third ed.: Lippincott Williams & Wilkins; 2013 [2]

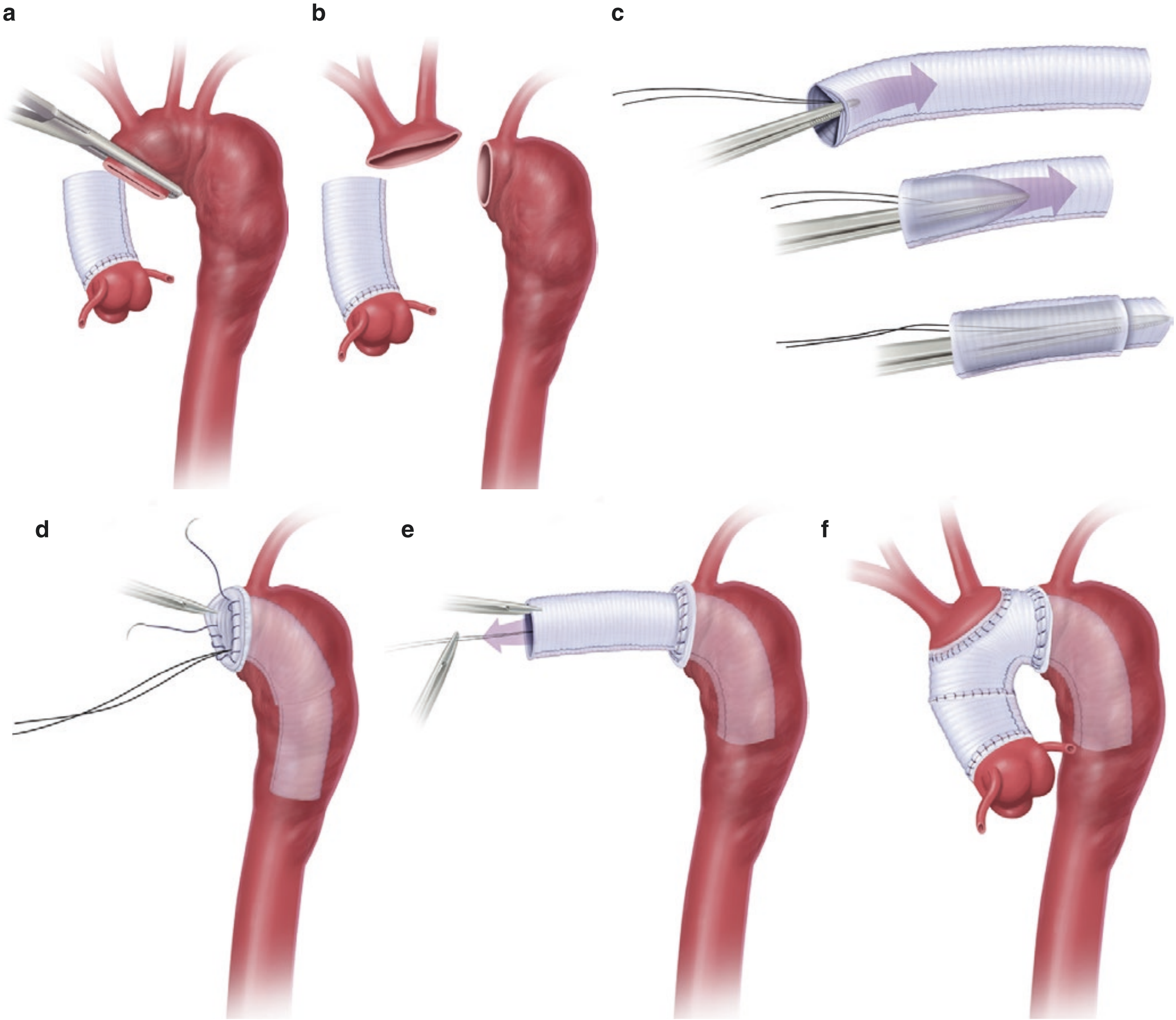


Fig. 57.13 (**a**) Proximal aortic work during the cooling phase; (**b**) Mobilization of the head vessels as a Carrel patch; (**c**) Elephant trunk manufacture; (**d**) Elephant trunk implantation and suturing; (**e**) Elephant trunk evagination; (**f**) Head vessels and graft to graft anastomosis. (Reprinted with permission from Velasquez CA, Zafar MA, Saeyeldin A, et al. Two-Stage Elephant Trunk approach for open management of distal aortic arch and descending aortic pathology in patients with Marfan syndrome. Ann Cardiothorac Surg 2017;6(6):712–720 [48])

Elephant trunk procedure is a two-stage approach for arch aneurysms that extend into the descending aorta. During the first stage, an 'elephant trunk' graft is sewn to the aortic arch with its distal end hanging freely in the descending aorta. The second stage is done about 4 weeks later, in which the descending aneurysm is resected and the distal end of the elephant trunk is attached to the normal aorta below (Figs. 57.13, 57.14, and 57.15) [40].

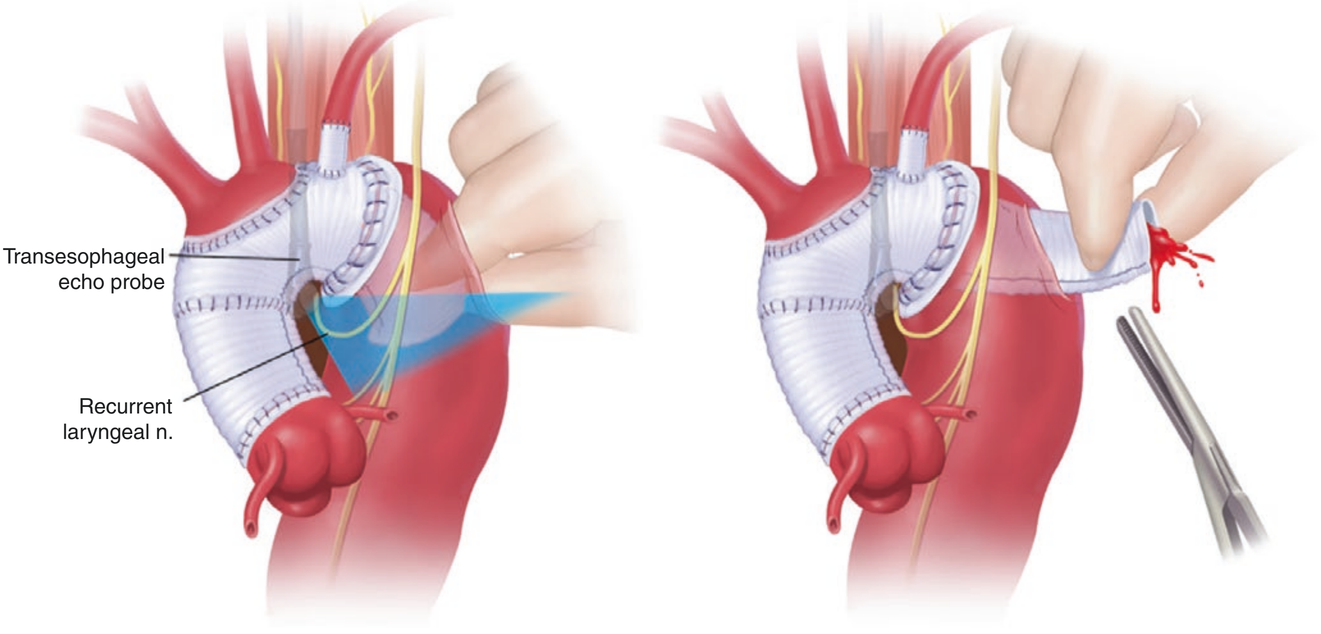
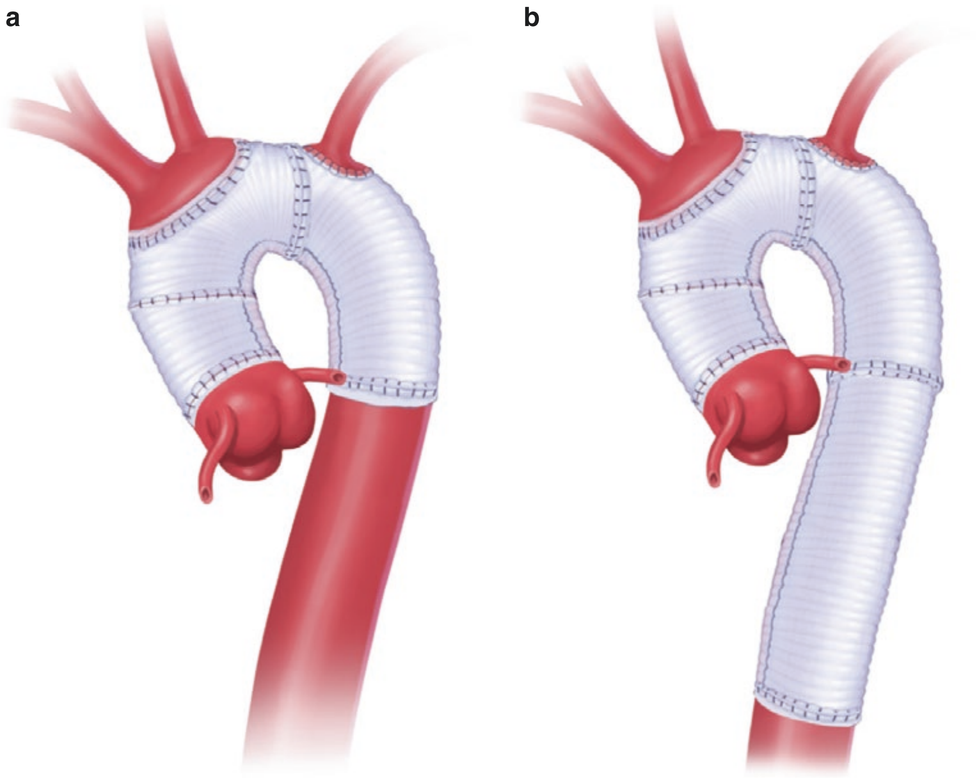


Fig. 57.14 Finger-thumb technique for retrieval of the elephant trunk. (Reprinted with permission from Velasquez CA, Zafar MA, Saeyeldin A, et al. Two-Stage Elephant Trunk approach for open management of distal aortic arch and descending aortic pathology in patients with Marfan syndrome. Ann Cardiothorac Surg 2017;6(6):712–720 [48])

Fig. 57.15 Completion of the elephant trunk procedure. (**a**) Anastomosis to the descending aorta; (**b**) Replacement of the thoracoabdominal aorta. (Reprinted with permission from Velasquez CA, Zafar MA, Saeyeldin A, et al. Two-Stage Elephant Trunk approach for open management of distal aortic arch and descending aortic pathology in patients with Marfan syndrome. Ann Cardiothorac Surg 2017;6(6):712–720 [48])



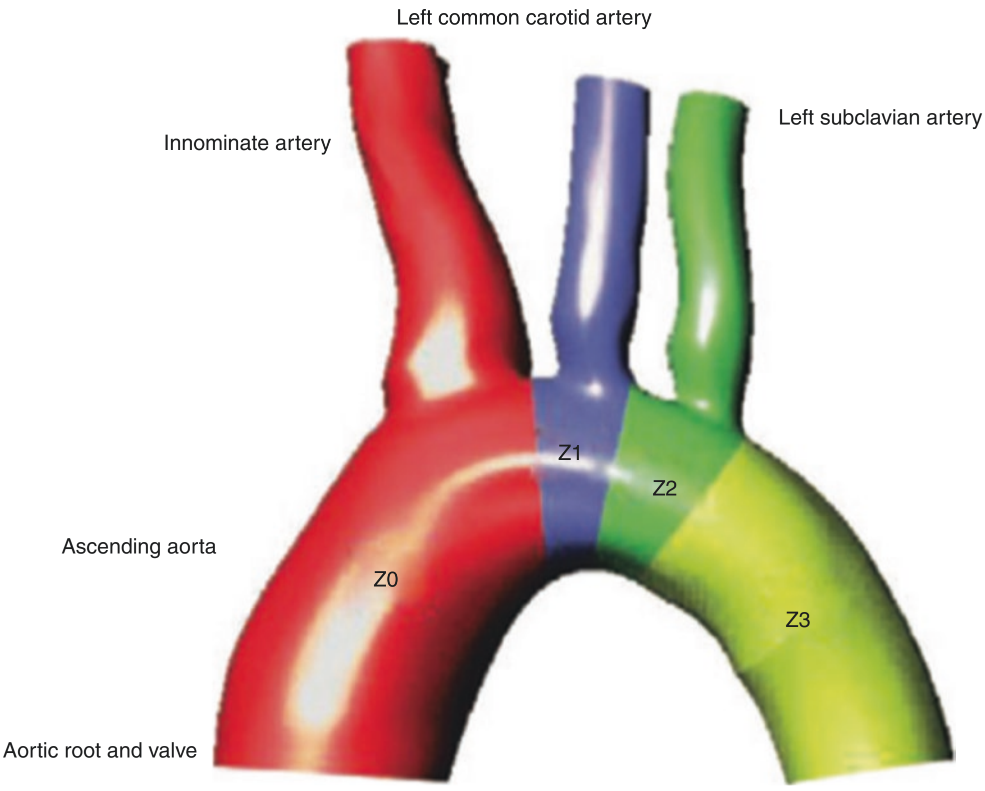


Fig. 57.16 Ishimaru landing zone classification. (Reprinted with permission from Szeto WY, Bavaria JE. Hybrid Repair of Aortic Arch Aneurysms: Combined Open Arch Reconstruction and Endovascular Repair. Sem Thorac Cardiovasc Surg 2009;21(4):347–54 [49])

Endovascular repair for arch aneurysms remains a possibility for patients who are poor surgical candidates for open repair, however custom-made devices take considerable time to prepare and are not generally available at present for emergent and urgent cases. The risk of stroke is as high as with conventional open surgery [42].

For the purpose of endovascular repair, the aortic arch is classified into four landing zones based on the Ishimura classification [43]. These are: zone (Z) 0, ascending aorta to innominate artery; Z1, innominate artery to left common carotid artery; Z2, left common carotid artery to subclavian artery and Z3, left subclavian artery to proximal descending thoracic aorta, for endovascular repair (Fig. 57.16) [43]. Stents require a minimum of 15 mm of landing zone proximally and distally for the placement of the endograft, but the requirement increases to 20 mm in a highly angulated arch. Ideal sealing zone parameters for the arch are: aortic diameter smaller than 40 mm, length of disease-free aorta greater than 20 mm and an angulation of less than 60° [44].

Some techniques for total endovascular repair include branched endografts, parallel stent graft technique and in situ fenestration [42]. Specific arch branch devices are under investigation for branched endograft repair. These include devices from Cook (Cook Medical, Bloomington, IN), Bolton (Bolton Medical, Sunrise, FL) and Medtronic (Medtronic, Santa Rosa, CA) [45].

Hybrid techniques have been developed using a combination of open and endovascular approaches. These aim at reducing postoperative mortality and morbidity. For elderly patients and those with significant comorbidities, these techniques provide an alternative approach [39].

Type I hybrid repair is ideal for patients in whom the arch pathology extends into the descending thoracic aorta, but the ascending aorta needs to have a normal diameter for the proximal attachment of the stent graft. The arch vessels are debranched and moved to the proximal ascending aorta with subsequent endovascular repair of the arch aneurysm. Cardiopulmonary bypass and circulatory arrest are not typically required for a Type I repair [39]. Aortic dissection occurs not uncommonly from the side biting clamp on the ascending aorta.

When an aneurysm involves the ascending aorta and aortic arch, a Type II hybrid procedure may be considered. The ascending aorta is replaced, with aortic arch vessel debranching and TEVAR, and the proximal landing zone is located in the replaced ascending aorta. The distal arch and descending thoracic aorta do not need to be exposed and the time of circulatory arrest is shorter as compared to total arch replacement or elephant trunk techniques. A Type III hybrid procedure is indicated for patients with aneurysms involving the entire thoracic aorta (ascending, arch and descending thoracic aorta). It is a two-stage approach. Stage 1 is an open or stented elephant trunk procedure and stage 2, done after an interim period, involves a retrograde thoracic aortic endovascular repair (TEVAR) (Fig. 57.17) [39].

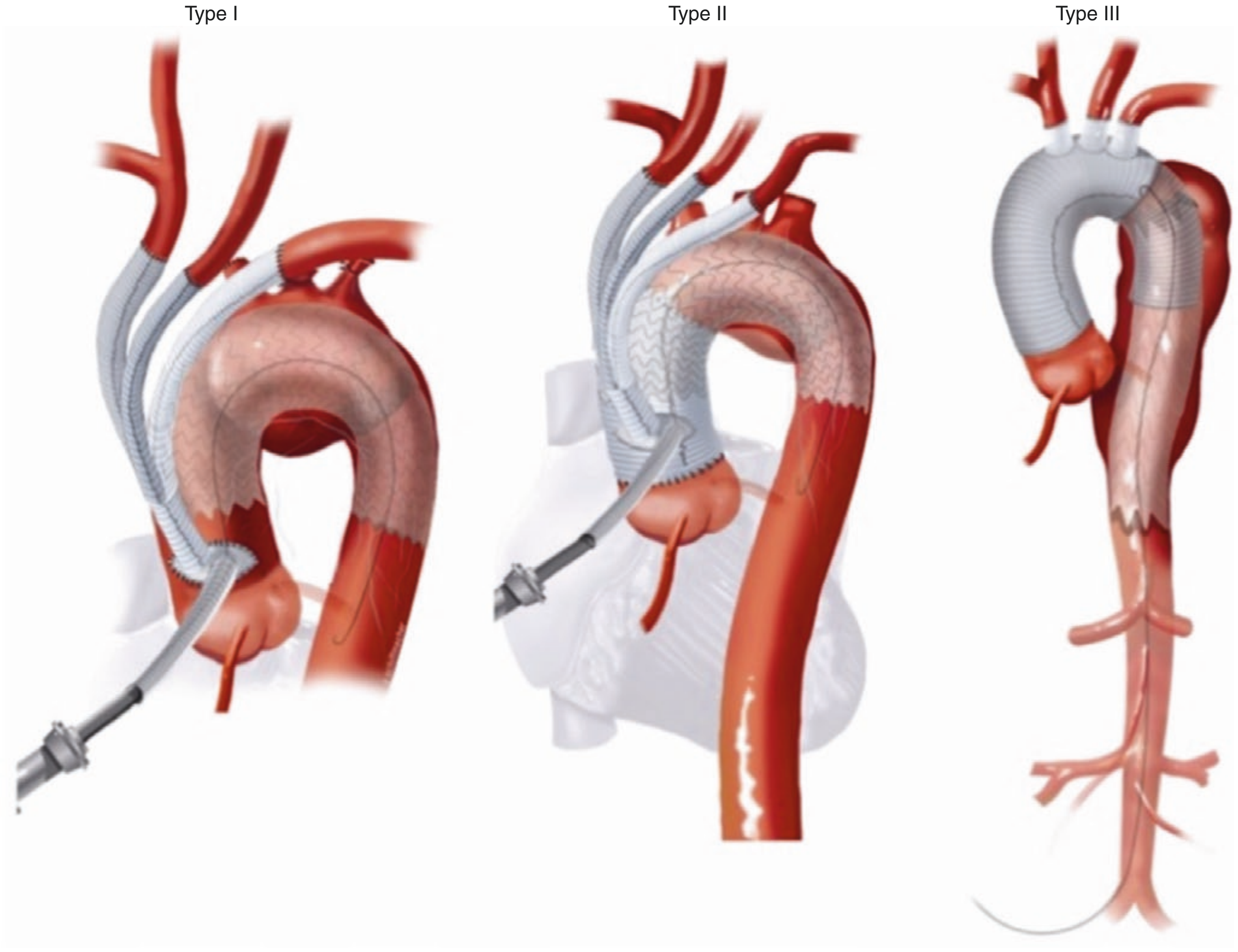


Fig. 57.17 Hybrid procedure classification. Type I, Type II and Type III hybrid repair. (Reprinted with permission from Szeto WY, Bavaria JE. Hybrid Repair of Aortic Arch Aneurysms: Combined Open Arch Reconstruction and Endovascular Repair. Seminars in Thoracic and Cardiovascular Surgery. 2009;21(4):347–54 [49])

Custom made devices using single or multiple side branches for the vessels coming off the arch are being used for investigational arch repair [46, 47] These devices require a healthy proximal landing zone and have a higher reported risk of stroke, limiting their present use. With further development, endovascular repair of arch aneurysms may become the mainstay of treatment for the elderly in the future [3].

Conclusion

Aortic aneurysms limited to the aortic arch are a rare entity and most are the result of distal extension of an ascending or a proximal extension of a descending aneurysm. Certain anomalous aortic arch vessel branching patters, such as bovine arch, are associated with an increased risk of thoracic aortic aneurysm and patients with these variations may warrant periodic surveillance for thoracic aortic aneurysm. Arch aneurysms are mostly asymptomatic; however, some can present with symptoms from compression of the adjacent structures or with excruciating pain, in the event of a dissection.

The aortic arch and adjacent structures can be visualized by CT or MRI. Surgical intervention is required if the patient is symptomatic (with pain) or when an asymptomatic patient meets the size criterion of 5 cm or more.

Total arch repair remains the standard of treatment for arch aneurysms. Elephant trunk procedures are also commonly done, facilitating later care of the adjacent descending aorta. Special considerations must be taken for cerebral protection during any type of surgical intervention involving the arch. Advanced endografts and hybrid techniques for arch repair are under development with hopes of application in high risk, elderly patients who cannot safely undergo the standard open repair.

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58

Hybrid Aortic Arch Repair

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High Yield Facts

- Conventional, open arch surgery is nowadays challenged by the introduction of hybrid aortic arch repair strategies including the frozen elephant trunk (FET) procedure.
- Modern hybrid arch procedures reduce the invasiveness of arch surgery and facilitate a single-staged approach in patients with extensive disease of the aortic arch and descending aorta.
- Various hybrid stent grafts combined with branched supra-aortic vessel grafts and debranching procedures have been introduced and are applied depending on the underlying aortic pathology, extent of the disease and surgeon's preference.
- Hybrid aortic arch surgery using the FET technique requires the use of cardiopulmonary bypass and hypothermic circulatory arrest with selective brain perfusion.
- Clinical results of hybrid aortic surgery are currently based on data from large registries and single center reports and support the efficacy and safety of this approach.
- Total endo-prosthetic arch repair is currently under clinical investigation as hybrid technologies and devices improve further.

Introduction

Surgical treatment of the aortic arch through a median sternotomy has been performed for over five decades and has nowadays become an integral part of aortic surgery [1–4]. Depending on the extent of the disease and repair, the so-called "hemiarch" or "full arch" replacement with common vascular grafts and reinsertion of the supra-aortic vessels is routinely performed under hypothermic circulatory arrest and selective cerebral perfusion with excellent results (Fig. 58.1). Since the first description by Borst et al. in 1983 the introduction of the classical elephant trunk technique (ET) allowed not only to address the aortic arch pathology but also the jeopardized descending aorta [5]. The classical ET technique consisted of a vascular graft extending from the distal aortic arch into the proximal descending aorta, giving rise to the term "elephant trunk", and, thereby, preparing a second stage surgical intervention for repair of the descending aorta through a thoracotomy (Fig. 58.2a) [4, 5].

This technique was later modified by Svensson and coworkers [6], but it was again the group from Hannover that advanced the well-established classical elephant trunk to the frozen elephant trunk (FET) technique into clinical practice by combining the concepts of the classical elephant trunk with endovascular stenting of the descending aorta [7]. In their publication from 1993, Karck and coworkers [7] introduced a hybrid stented graft prosthesis that combined a covered stent at its distal portion sutured to the proximal end of a conventional tube graft. Thus, stenting of the descending aorta was made feasible by expansive radical forces of the frozen elephant trunk while enabling a classical full arch replacement at the same time (Fig. 58.2b, c).

Later, a commercially available hybrid graft was introduced by Jakob from Essen in Germany [8, 9]. This non-branched, hybrid graft enabled the treatment of patients with complex aortic pathologies and allowed a single-staged treatment of certain pathologies within the descending aorta without the need for a subsequent procedure. It was Kazui and later Shrestra et al. that reported the use of a modified four-branched hybrid prosthesis for supra-aortic vessel revascularization and arterial body perfusion during cardiopulmonary bypass [10, 11].

Since the commercial introduction of various grafts (Fig. 58.3), the hybrid aortic arch repair (FET) has become

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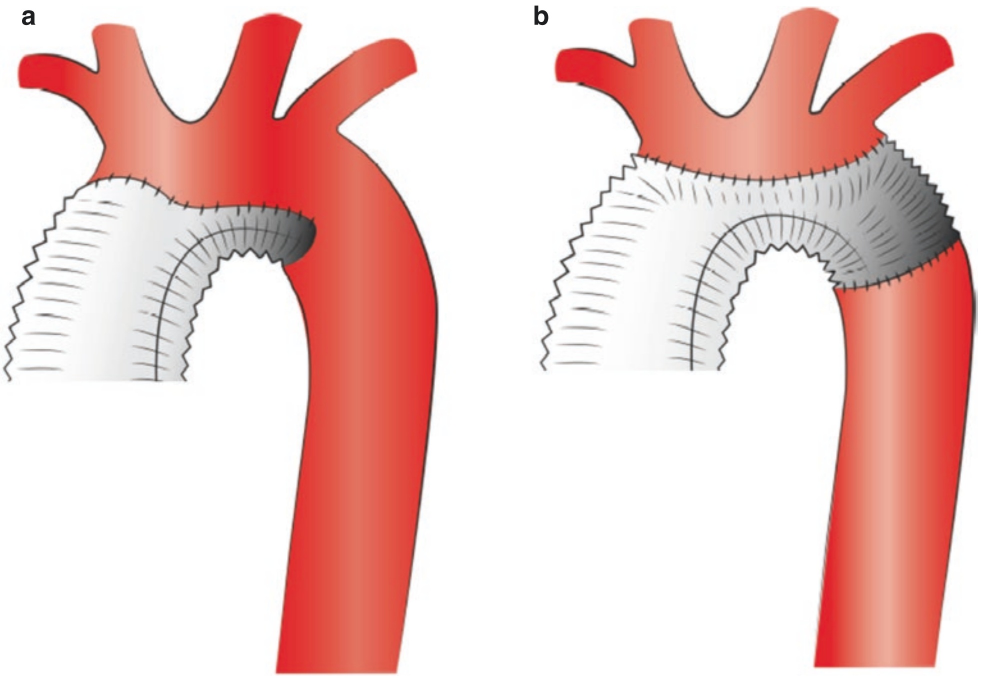

Fig. 58.1 The "hemiarch" (**a**) or "full arch" replacement (**b**) with common vascular grafts and reinsertion of the supra-aortic vessels is routinely performed under hypothermic circulatory arrest and selective cerebral perfusion

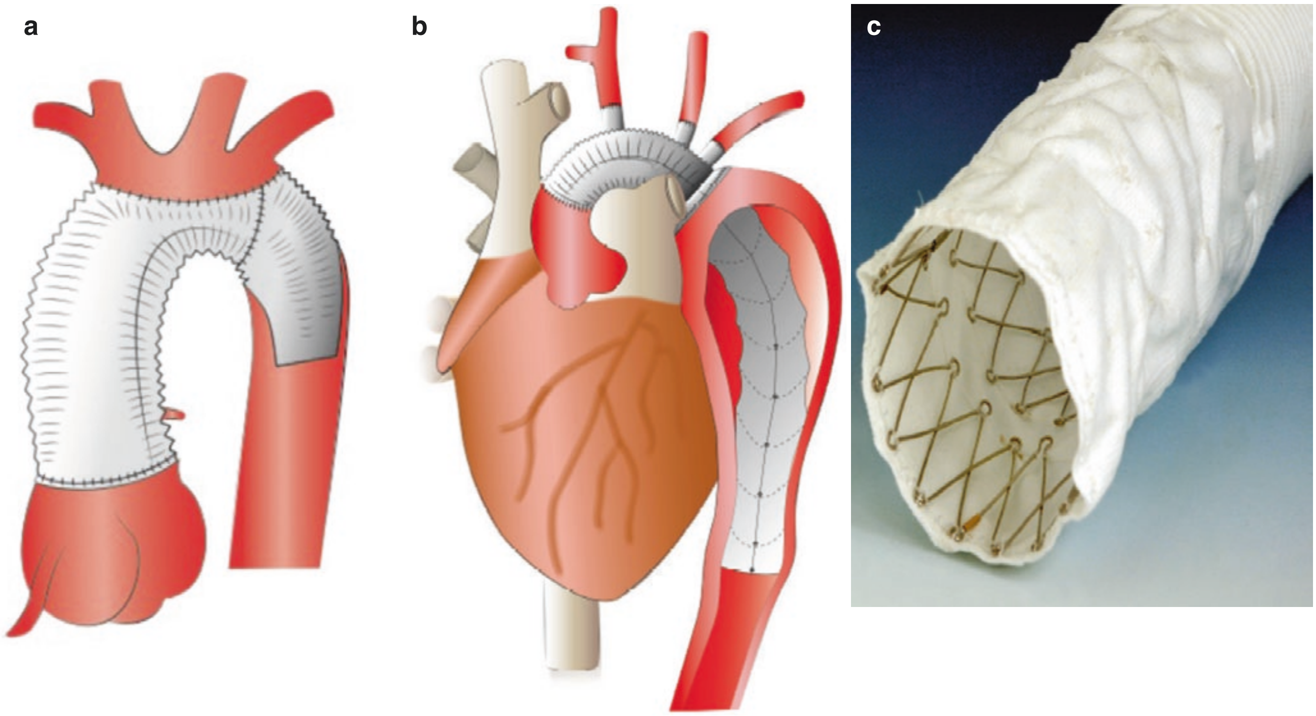

Fig. 58.2 The "classical" (**a**) and "frozen" elephant trunk (**b**) prosthesis for aortic arch repair. One of the first available FET prosthesis, the Chavan-Haverich endograft from Hannover (**c**), consisted of a Dacron vascular prosthesis with stainless-steel stents affixed at its distal end. With kind approval by Professor Dr. A. Haverich

increasingly popular as a valuable alternative to the classical elephant trunk technique. The concept of hybrid repair includes complete replacment of the diseased aortic arch, restoring the supra-aortic vessel perfusion and extending the aortic repair into the diseased descending aorta and, thereby, achieving a satisfactory sealing of the diseased aorta with the hybrid stent graft. Thus, similar to the conventional elephant trunk technique, the FET technique enables in certain pathologies a single-staged procedure or paves the way for a two-staged repair by providing a secure and easy landing zone for

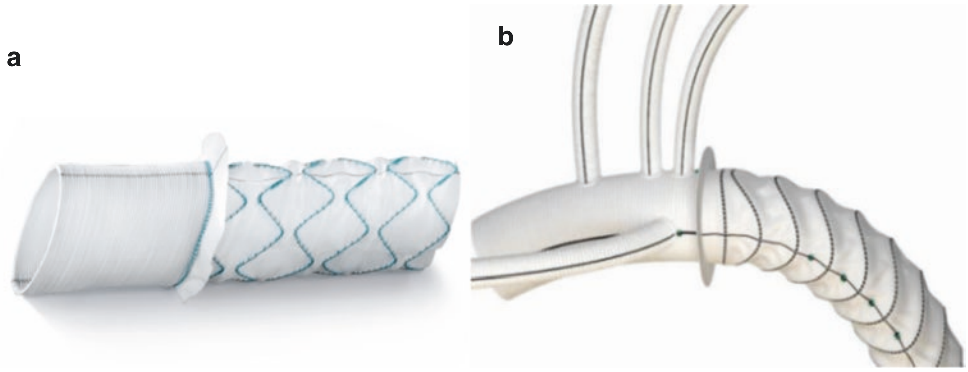

Fig. 58.3 The two most widely used grafts in Europe for hybrid arch repair. The E-vita OPEN PLUS® Hybrid stent-graft prosthesis is a straight tube graft without branches and a Z-shaped nitinol stent (**a**). With kind approval of Jotec, Hechingen, Germany. The Vascutek Thoraflex® Hybrid stent-graft (**b**) has four branches for selective anastomosis of the supra-aortic vessels and an arterial inflow graft that enables faster body perfusion after completion of the distal anastomosis and reduces circulatory arrest time. With kind approval from Vascutek Inchinnan, Scotland

a subsequent thoracic endovascular aortic repair (TEVAR) of the remaining descending aorta. For that reason, treatment of the aortic arch is currently evolving towards the "new *frontier"* of hybrid arch repair.

Indications and Patient Selection

The indications for the use of the FET technique are currently under constant evaluation but commonly include acute or chronic type A or B dissections with the primary entry in the arch or proximal descending aorta, complex aneurysms of the arch and descending aorta, or penetrating aortic ulcers [12–14].

The FET procedure in aortic dissections with intimal tear or reentry in the aortic arch or proximal descending aorta offers beyond a complete aortic arch replacement, a high rate of early (<3 months) and late (>6 months) false lumen thrombosis in over 80% of patients, thereby, promoting aortic remodeling and reducing distal malperfusion syndromes [14]. Residual dissection flaps and/or perfused false lumen of the downstream aorta are frequently observed in the arch or descending thoracic aorta after conventional, mostly limited, aortic arch repair that may subsequently lead to a distal malperfusion syndrome. Later on, a sequela of false lumen dilatation, aneurysm formation or even rupture can be observed. Thus, hybrid aortic arch surgery using the FET is recommended in this setting in the latest guidelines of the European Society of Cardiology for the treatment of Stanford type A acute aortic dissection with malperfusion (Table 58.1) and is also endorsed in the position paper of the Vascular Domain of European Association of Cardiothoracic Surgery [13, 14].

Additional indications for the hybrid FET approach include post-dissection aneurysmal formation of the arch after repair of Type A dissection, retrograde type A dissections after TEVAR and any type of complex aortic aneurysms that would otherwise require a two-staged approach.

Table 58.1 Current indications for the FET procedure modified according to the ESC guidelines and the EACTS vascular domain position paper[a]

Recommendations	Class	Level
In patients with acute type A AD with a primary entry in the distal arch or proximal descending aorta with organ malperfusion or to prevent organ malperfusion	IIa	B/C
In patients with acute type A AD to prevent mid-term aneurysmal formation in the downstream aorta	IIb	C
In complicated acute Type B AD when primary TEVAR is not feasible or the risk of retrograde type A AD is high	IIa	C
In extensive thoracic and thoracoabdominal aortic disease when a second-staged approach is anticipated (TEVAR, open surgery)	IIa	C

AD aortic dissection, *TEVAR* thoracic endovascular aortic repair

[a] References [13, 14]

Similarly, the currently proposed contraindications for the use of the FET procedure are not absolute and also under clinical investigation. As the experience with the FET procedure is constantly increasing, certain pitfalls or technical limitations have been recognized or solved that may interfere with the performance of a safe and efficient FET procedure [14, 15]. Severe aortic kinking or a tortuous aorta, older age, multiple comorbidities and major neurological deficits especially in acute aortic dissection, can be considered as relative contraindications [14–17].

Operative Technique

Detailed analysis of the underlying aortic pathology is crucial for adopting the adequate surgical strategy. Preprocedural examination including coronary angiography, echocardiography, thoracic X-ray and Doppler sonography of the carotids should be performed in all elective patients. A high-resolution computed tomography (CT) scan of the complete thoracoabdominal aorta is required to verify the extent of the aortic disease and/or to detect the location of the primary entry site and potential re-entries, true and false lumen perfusion and the supra-aortic or distal vessel perfusion in acute aortic dissection. The proper sizing and distal landing zone of the FET can be evaluated intraoperatively by angioscopy, but also in preoperative CT scans by measuring the aortic diameter at the distal landing zone of the FET. This can be measured from the site of the distal anastomosis of the hybrid graft downwards to the descending aorta [18]. The length of the current FET prosthesis ranges between 10 and 16 cm. Oversizing is usually not recommended in patients with aortic dissections to avoid new intimal tears or even vessel perforation but can be tolerated in some cases of extensive aneurysms [18].

The techniques of hybrid aortic arch repair are numerous and highly variable depending on the underlying aortic pathology as well as surgeons' experience and preference [1, 4, 9, 14]. The strategy ranges from total endovascular arch repair after previous debranching of the supra-aortic vessel to the FET procedure with or without multibranched grafts for supra-aortic revascularization or extraanatomical bypass grafts to the left subclavian artery or axillary artery. The underlying principle in all procedures is to create a safe proximal aortic anastomosis of the FET and, if needed, to facilitate a landing zone for a subsequent TEVAR procedure.

The Criado classification has gained wide acceptance in order to classify the different hybrid techniques of aortic arch repair [19]. Four different zones (Fig. 58.4) within the aortic arch are described that can be used based on the surgeons' strategy, extent of disease and patient's anatomy. Zone 0 is located proximal to the innominate artery, zone 1 proximal to the left common carotid artery, zone 2 between the left carotid and subclavian artery and zone 3 distal to the left subclavian artery and extending into the descending aorta. Depending on the chosen proximal landing zone of the FET, revascularization of the supra-aortic vessels is usually performed either by a direct implantation or via seperate revascularization with a multibranched hybrid aortic stent graft (zone 3) or multibranched/single vessel grafts (zone 0–2).

The following steps briefly describe our approach of a Zone 3 FET procedure using an E-vita Jotec hybrid prosthesis (Jotec, Hechingen, Germany) with direct "en bloc" reimplantation of the supra-aortic vessels. As aforementioned the preferred cannulation site, type of cerebral or myocardial protection and temperature of hypothermic arrest is highly variable in the literature and is discussed elsewhere.

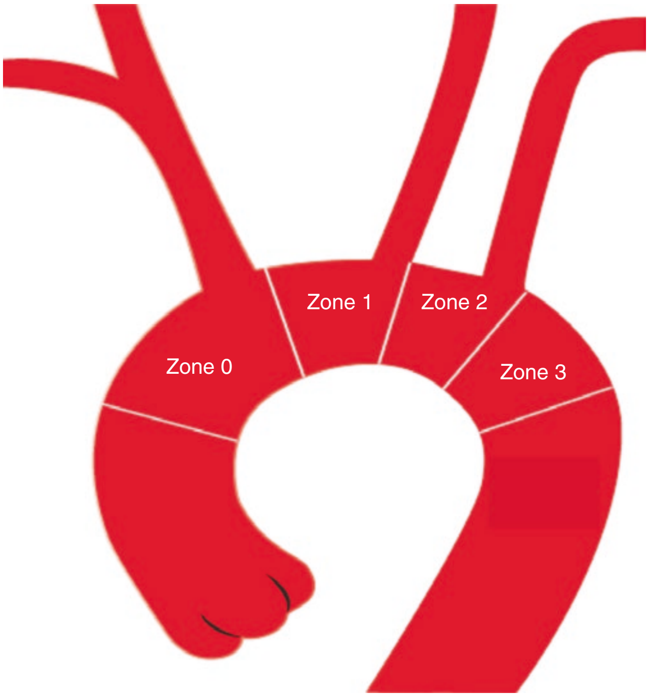

Fig. 58.4 The zones of the aortic arch adopted from the classification by Criado et al. [19]. Zone 0 – before the innominate artery; Zone 1 – between the innominate artery and left common carotid artery; Zone 2 – between the left common carotid and subclavian artery; Zone 3 – distal to the left subclavian artery

1. *Cardiopulmonary bypass (CPB) and cardiocerebral protection*: The right axillary artery is used in most cases after previously excluding a dissection of the vessel. It offers the advantage of antegrade perfusion of the aorta and right-lateral cerebral perfusion during circulatory arrest. We prefer the direct cannulation of the axillary artery using a purse string suture and Seldinger technique (Fig. 58.5a). Venous cannulation is usually performed after sternotomy through the right atrium. Alternative arterial access routes include the carotid artery, innominate artery, the femoral artery or direct aortic cannulation. After CPB is established cooling is initiated to moderate hypothermia with a target nasopharyngeal temperature of 25–28 °C.
2. The aortic arch and the origin of the supra-aortic vessels are then dissected (Fig. 58.5b). After reaching the target body temperature the aorta is clamped and cold blood cardioplegic cardiac arrest established either through the antegrade, selective or retrograde route. Cardioplegic delivery is repeated every 20 min to maintain arrest.
3. Unilateral cerebral perfusion is initiated after clamping of the innominate artery. Then the aortic arch is opened and bilateral, selective, antegrade cerebral perfusion employed after direct catheterization of the left carotid artery. The aortic arch is resected to the plane of the distal anastomosis

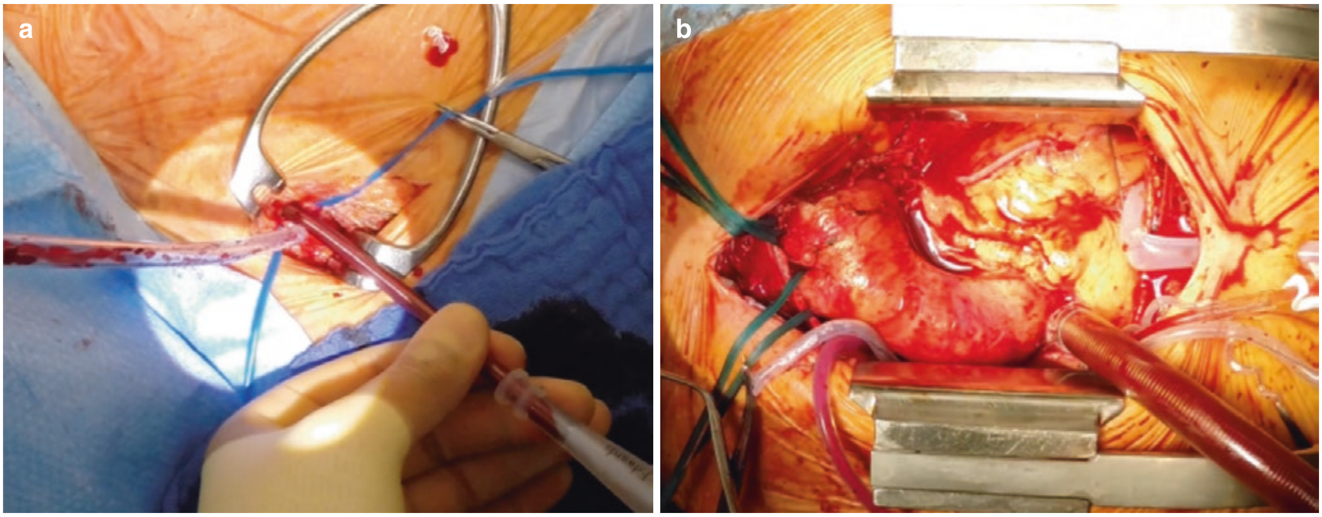

Fig. 58.5 Direct cannulation of the right axillary artery using a pursue string suture with 5–0 Prolene and introducing a flexible arterial cannula with the Seldinger technique (**a**). Venous cannulation is performed after sternotomy through the right atrium. A left ventricular vent is placed and a retrograde cardioplegia catheter introduced into the coronary sinus. Then the ascending aorta, the aortic arch and the origin of the supra-aortic vessels are dissected (**b**)

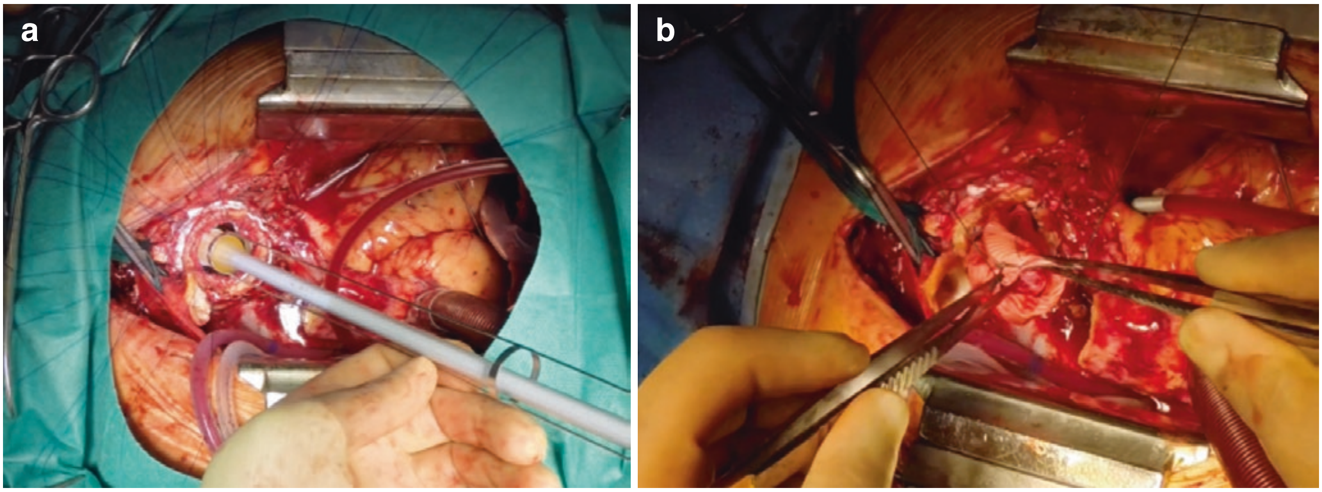

Fig. 58.6 The aortic wall for the distal anastomosis is reinforced with felt stripes and/or U-shaped pledged sutures, especially in aortic dissections (**a**). Then the stent graft is introduced, and the stent released while taking care that the collar of the hybrid prosthesis remains in the plane of the distal anastomosis. After completing the distal anastomosis the proximal part of the hybrid graft is retrieved and unfolded (**b**)

(Zone 3) and the supra-aortic vessel island prepared for the "en bloc" reinsertion using the "island" technique.

4. We usually reinforce the wall of the aortic stump with felt stripes and/or U-shaped pledged sutures, especially in acute or chronic dissections (Fig. 58.6a). Then the stent graft is inserted into the "true" lumen and the stent is released in a stepwise fashion. Care should be taken to avoid any dislocation of the collar of the prosthesis from the plane of the distal anastomosis. A transfemoral wire can be used to ensure proper positioning of the hybrid graft in the true lumen [20, 21]. Optimal positioning in the distal landing zone can also be ensured by angioscopy of the aorta before deploying the stent graft [20].
5. After stent release the distal anastomosis is performed between the collar of the hybrid prosthesis and the aorta either with a running 3–0 Prolene suture or the the U-shaped sutures and the proximal part of the hybrid graft is retrieved (Fig. 58.6b). This anastomosis becomes easier when a more proximal landing zone (zone 0–2) is chosen. Then single or multibranched grafts must be used for revascularization of the respective supra-aortic vessels, usually the left subclavian artery.
6. Arch replacement is completed with the proximal part of the FET tube graft by "en-bloc" reinsertion of the supra-aortic vessel with the island technique when a non-branched prosthesis is used (E-vita, Jotec, Fig. 58.7a).

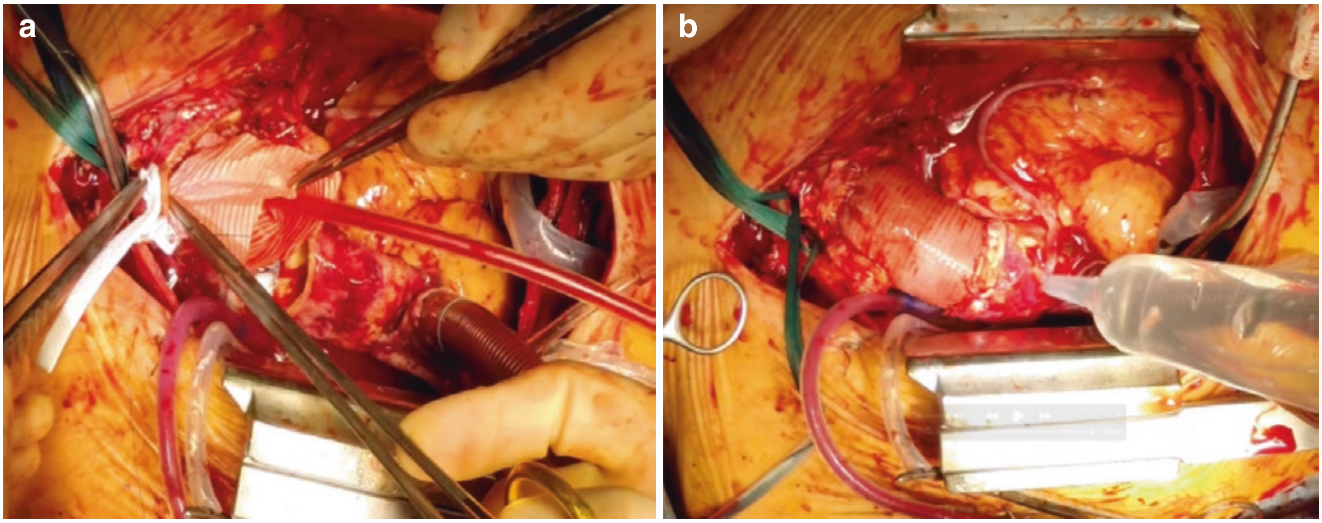

Fig. 58.7 The "en-bloc" reinsertion of the supra-aortic vessel is performed with a 4–0 Prolene suture and felt stripes (**a**). Then the proximal tube graft is sutured to the ascending aorta with a 3–0 or 4–0 Prolene running suture (**b**)

In case of a multi-branched prosthesis (Thoraflex, Vascutek, Inchinnan, Scotland), the supra-aortic vessels are revascularized separately with the predefined branches. This approach offers the advantage of early low body reperfusion via the arterial inflow side branch of the hybrid graft after completion of the left subclavian artery anastomosis. Finally, the proximal tube graft is sutured to the ascending aorta (Fig. 58.7b).

Table 58.2 Reported results after the hybrid FET procedure

Outcome	Incidence (%)
Hospital death	8–11
Stroke/TIA	4–8
Reoperation for bleeding	8–15
Spinal cord injury	4–9
Endoleaks	4–9
False lumen stenting, stent graft perforation	<5

FET frozen elephant trunk, *TIA* transient ischemic attack

Clinical Outcomes

The clinical benefits of FET procedure for treatment of aortic arch disease in comparison to the classical ET are controversially discussed in the literature [4, 22]. However, the FET procedure offers the advantage of avoiding a second-stage procedure in certain diseases and false lumen thrombosis is often observed at early and late follow-up after treatment of aortic dissections [14]. Although the experience with the FET hybrid procedures is constantly growing, the evidence is still based on data from large registries or single center reports and not randomized trials [4, 14]. In a recent systematic review of over 841 hybrid procedures Chakos and coworkers [22] reported an 8% hospital mortality, 7% stroke rate and 4% spinal cord injury rate (Table 58.2). In other systematic reviews early mortality ranged between 8% and 11%, cerebrovascular events between 4% and 7% and spinal injury between 4% and 7% [23, 24]. In addition, long-term survival was up to 75% at 7 years after FET implantation [22]. In the international E-vita OPEN-Plus registry the FET procedure was associated with 18% mortality in 350 patients with aortic dissection and 13% mortality in 159 patients with thoracic aneurysms. Stroke rate was 8% and spinal cord injury occurred in 8% of all patients, especially in patients with a distal landing zone of the FET lower than T10 [25]. Similarly, five-year survival after FET implantation was 75% in another single center series with a total of 286 patients [26].

Despite the potential benefits of the FET technique over the classical ET technique for aortic arch repair, it is still associated with some significant perioperative complications (Table 58.2), such as spinal cord injury, recurrent nerve palsy or endoleaks [14, 16, 23–25]. Consequently, deliberate use of this innovative procedure should be avoided since the clinical outcomes reported so far are not clearly superior to the conventional ET technique [4, 14, 22].

Conclusion

The FET technique is an intriguing and innovative hybrid procedure for aortic arch repair that has gained wide acceptance in the cardiovascular community. Latest advances in hybrid technology aiming at a total endovascular arch repair strategy are under clinical investigation and will further reshape the future of aortic arch repair.

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Endovascular Stent Grafting of Thoracic Aorta

59

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and Ali Khoynezhad

High Yield Facts

- TEVAR has evolved over the past 20 years as an attractive alternative to open surgical repair in patients with various aortic pathologies including dissection, aneurysms, penetrating ulcers, and blunt aortic injury.
- Hybrid aortic repairs exist for those who have physiologic or anatomic constraints.
- Complications of TEVAR include endoleak formation, vascular access complications, neurologic issues, and retrograde type A dissection.

Introduction

The application of endovascular techniques utilizing stent graft technology has evolved rapidly and changed the treatment paradigm of aortic diseases. Parodi and coworkers first demonstrated the feasibility of endovascular exclusion of abdominal aortic aneurysms in 1991 in a small clinical series which described the use of stent-anchored knitted Dacron grafts to treat abdominal aortic aneurysms [1]. The development and adoption of endovascular therapy for the treatment of descending thoracic aortic aneurysms soon followed the promising use of this revolutionary technology. Dake and coauthors reported the first series of endovascular treatment for descending thoracic aortic aneurysms in 1994 [2, 3]. White and coworkers performed the first thoracic aorta endovascular repair (TEVAR) for chronic type B aortic dissection in 1999 [4].

In 2005, the US Food and Drug Administration (FDA) approved the first commercially available stent graft for thoracic endovascular aortic repair (TEVAR) for the treatment of descending thoracic aortic aneurysms (Gore TAG, Gore and Associates, Inc., Flagstaff, AZ) [5–7]. Two additional devices subsequently obtained FDA approval in 2008: Talent (Medtronic, Santa Rosa, CA) and TX2 (Cook, Inc., Bloomington, IN) [8, 9]. More recently, Bolton Relay Thoracic Stent-Graft with Plus Delivery System (Bolton Medical, Sunrise, FL) was FDA approved in 2012.

The feasibility and successful utilization of TEVAR has been established in selected patients for the treatment of various aortic pathologies including traumatic aortic injury, penetrating aortic ulcers, and aortic dissections. Potential advantages of TEVAR versus open surgery include shorter operative time, less blood loss, decreased need for general anesthesia, and shorter hospital stay [10–12]. TEVAR avoids cardiopulmonary bypass with the need for aortic cross-clamping and deep hypothermic circulatory arrest.

Preoperative Planning and Considerations

Aortic Arch Landing Zones

The aortic arch is commonly divided into five landing zones that are demarcated by the origins of the branch vessels [13]. Zone 0 is the distal ascending aorta including the innominate artery; Zone 1 is distal to the innominate artery including the left common carotid artery; Zone 2 is distal to the left common carotid artery including the left subclavian artery (LSA); Zone 3 is from the left subclavian artery to a point 2 cm distal; and Zone 4 is the descending thoracic aorta starting farther than 2 cm distal to the left subclavian artery (Fig. 59.1).

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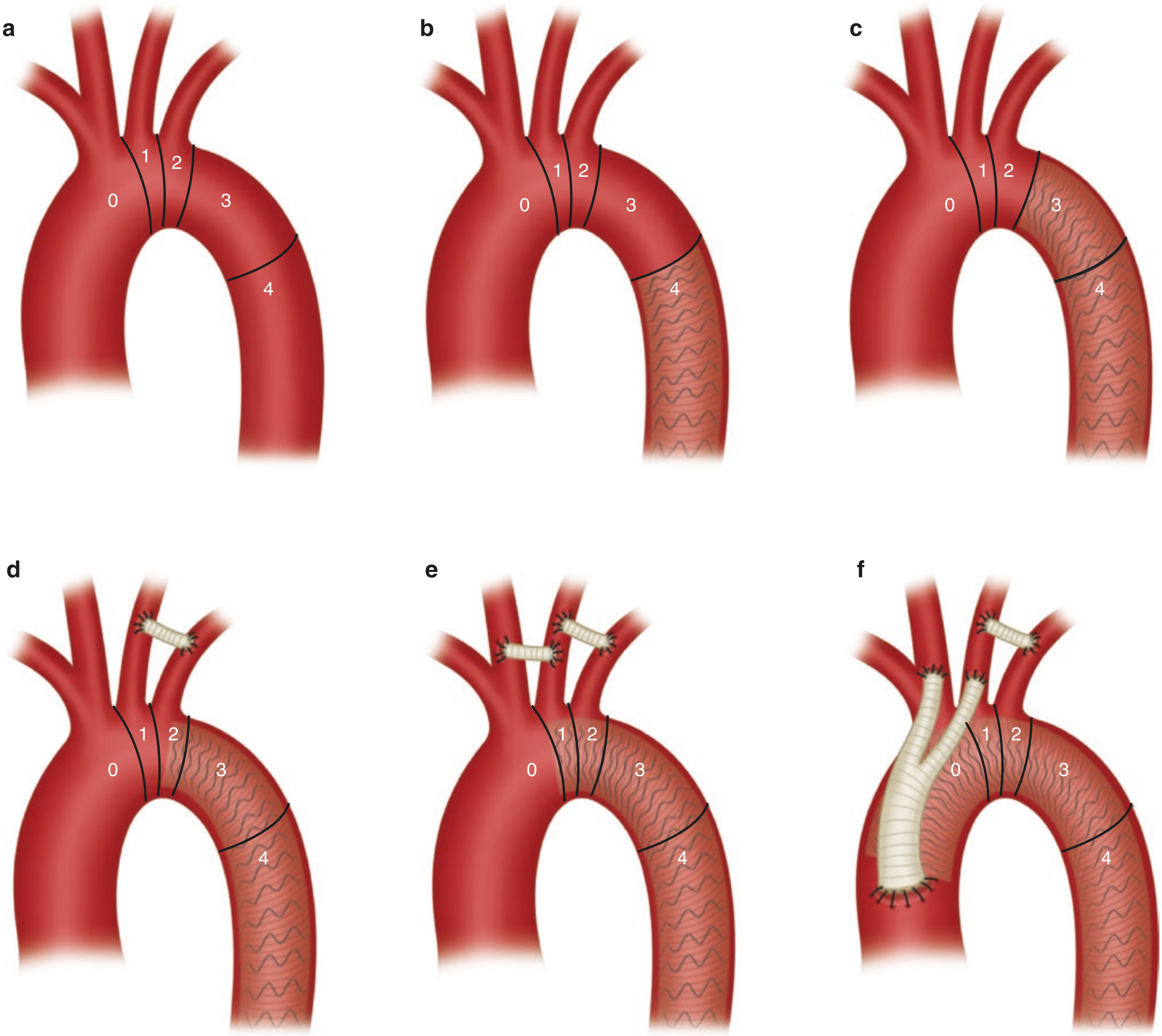

Fig. 59.1 (**a**) Distribution of landing zones for TEVAR. (**b**, **c**) Placement of a device in zones 3 or 4 does not require any revascularization. (**d**) Revascularisation of covered LSA with a left carotid-subclavian bypass. (**e**) Revascularisation of covered left carotid and subclavian arteries with a carotid-carotid and carotid subclavian bypass. (**f**) Complete revascularization of all aortic arch vessels with aorto-innominate and left carotid bypass as well as carotid-subclavian bypass

Cerebrospinal Fluid Drainage

The incidence of paraplegia or spinal cord ischemia (SCI) in various large published series of TEVAR performed for primarily aneurysmal disease has been reported between 0.6% and 4.3% [14–16]. Possible mechanisms for immediate SCI after TEVAR are coverage of critical intercostal or other collateral arteries that provide segmental blood flow to the spinal cord [15]. Perioperative hypotension may also lead to an inadequate spinal cord perfusion. SCI sequelae can range from monoparesis or paraparesis to paraplegia or quadriplegia, and can occur immediately or in a delayed fashion.

For these reasons, placement of preoperative CSF drainage in patients undergoing TEVAR should be strongly considered when:

1. Prior infrarenal aortic repair is present
2. Extensive coverage of thoracic aorta (>20 cm) is planned
3. Coverage of the lower segments of thoracic aorta (T8–L2 vertebrae levels) is planned
4. Coverage of LSA without revascularization is planned
5. Use of iliac conduit or hypogastric artery coverage is planned

Neuromonitoring

Neuromonitoring in patients undergoing TEVAR may be a useful intraoperative adjunct as it may identify patients who are at risk of SCI following stent graft deployment and in whom intraoperative maneuvers may be performed to optimize spinal cord perfusion via the collateral network. These maneuvers as described by Estrera include:

1. Increasing proximal aortic mean pressure to >80 mmHg
2. Decreasing CSF pressure by gravity drainage
3. Increasing hemoglobin levels by transfusion
4. Perform LSA revascularization if necessary to improve collateral blood flow to the spinal cord.

Vascular Access

The proper planning of vascular arterial access is critical in avoiding potential complications. The femoral artery must be of sufficient caliber to allow passage of the delivery sheath or endograft. If the femoral or external iliac arteries are of insufficient caliber to allow passage of the device, then a conduit to the common iliac artery may be constructed [17]. The iliac artery is exposed via a retroperitoneal exposure. A prosthetic conduit (10 mm Dacron or PTFE will accommodate the largest required sheath) is then used to perform an end to side anastomosis to the common iliac artery. The conduit is then tunneled percutaneously under the inguinal ligament through a femoral counter-incision and the distal segment of the conduit is then readily accessed.

TEVAR for Descending Thoracic and Thoracic Abdominal Aneurysms

The VALOR (Medtronic Vascular Talent Thoracic Stent Graft System for the Treatment of Thoracic Aortic Aneurysms) clinical trial enrolled 195 patients with descending thoracic aortic aneurysm (DTAA) undergoing TEVAR between 2003 and 2005 [8]. The results were compared to those obtained in 189 patients after OSR for DTAA. Patients received a mean number of 2.7 ± 1.3 stent graft components. In 33.5% of patients, the bare spring segment of the most proximally implanted device was in zones 1 or 2 of the aortic arch. Left subclavian revascularization was performed prior to TEVAR in 5.2%. The incidence of paraplegia was 1.5% and stroke 3.6%. The TEVAR group had better acute procedural outcomes compared to OSR ($p < 0.001$), decreased number of 30-day major adverse events (41% vs. 84.4%, $p < 0.001$), lower perioperative mortality (2% vs. 8%, $p < 0.001$), and decreased 12-month aneurysm related mortality (3.1% vs. 11.6%, $p < 0.002$), respectively.

This study demonstrates TEVAR to be a safe and effective alternative to OSR, with lower perioperative mortality and complications. However, sustained benefits on long term survival have not yet been proven [18], and randomized trials will be needed to address this question.

Open Debranching and TEVAR (Hybrid Aortic Repair)

Generally, patients with "physiological constraints", not being suitable candidates for open thoracoabdominal or aortic arch repair, are usually evaluated for TEVAR (including fenestrated and branched TEVAR), while patients with "anatomic constraints", not having proper proximal and distal landing zones, are considered for open repair. There is a cohort of patients, who are poor candidates due to physiologic and anatomic constraints that may benefit from open debranching followed by TEVAR exclusion of the branched-aortic portion (Fig. 59.2).

Branched and Fenestrated Grafts for TEVAR

Conventional open surgical techniques to repair thoracoabdominal aortic aneurysms (TAAA) have achieved excellent results in the modern era with the addition of intra-operative adjuncts including distal aortic perfusion, cerebrospinal fluid drainage, and passive moderate hypothermia with the overall incidence of neurologic deficits decreasing to approximately 2% [19, 20]. Due to the complexity of this procedure, endovascular techniques have been adopted for the treatment of TAAAs in patients who are at high risk for open surgical repair. If thoracic aneurysms require fixation or landing zones within the aortic arch or visceral segment of the aorta, endovascular repair requires either a hybrid two-staged operation with open surgical de-branching followed by endovascular graft exclusion or a single stage endovascular repair using either branched or fenestrated stent grafts.

TEVAR for Acute Thoracic Aortic Dissection

Uncomplicated Type B Dissection

Acute descending thoracic aortic dissection (Stanford type B) is a dramatic and potentially catastrophic condition. The current treatment of type B dissection remains medical [21] and the majority of patients with uncomplicated disease can be treated conservatively with anti-impulsive and antihypertensive therapy [22].

The Investigation of Stent Grafts in Aortic Dissection (INSTEAD) Trial was undertaken to determine if endovascular treatment might improve long-term outcome in patients with

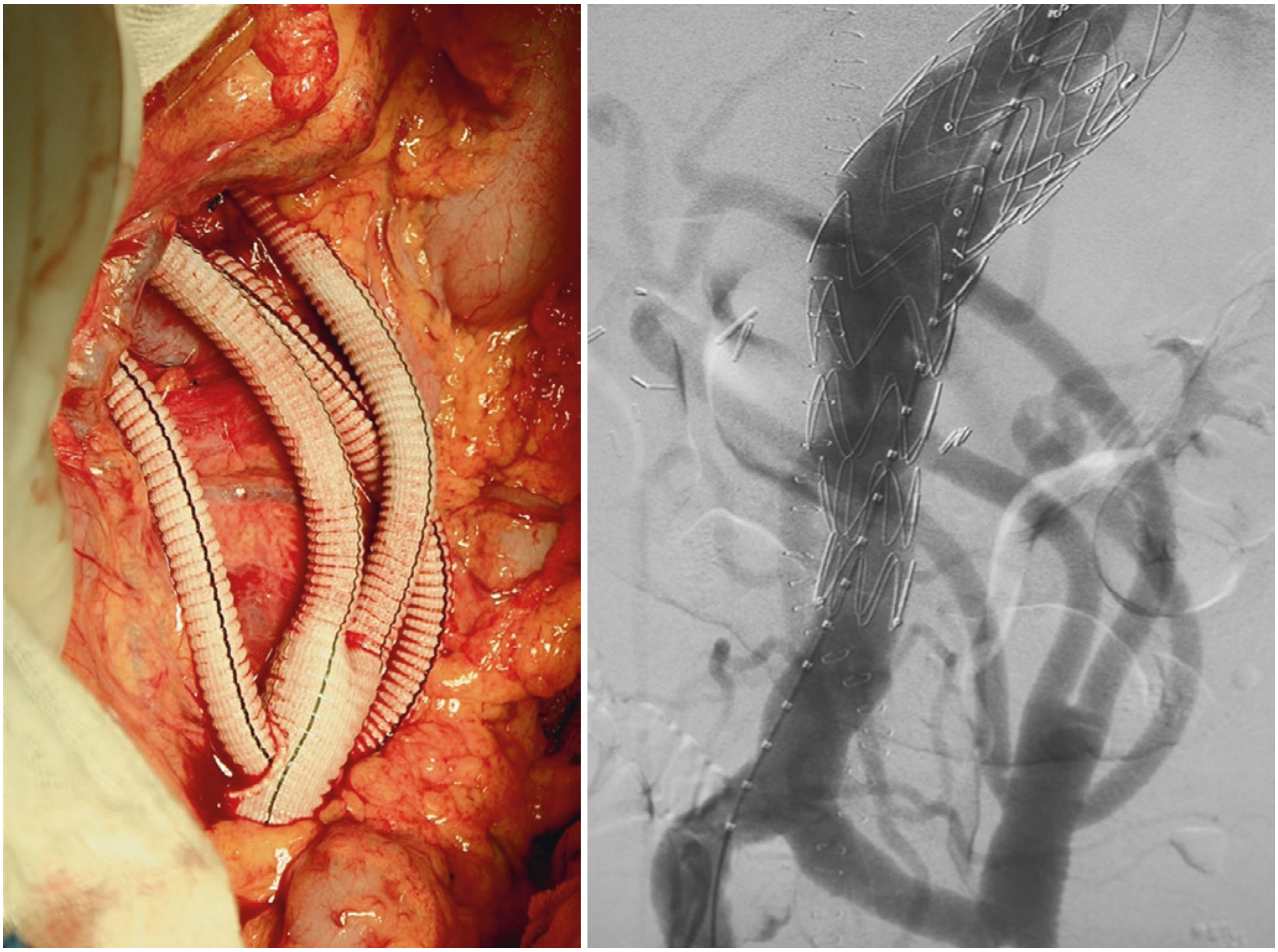

Fig. 59.2 Extra-anatomic bypass to celiac, superior mesenteric and both renal arteries coming off the left common iliac artery using a custom quadfurcated graft. Completion angiogram reveals patency of all bypassed grafts and exclusion of the aneurysm. Same custom graft can be used for total aortic arch hybrid repair

type B dissections [23]. This was a randomized trial in which 140 patients in stable clinical condition at least 2 weeks after the index dissection underwent either elective TEVAR in addition to optimal medical therapy or optimal medical therapy alone. The investigators found no difference in all-cause mortality or aortic related mortality between the two groups; the 2-year survival rate was 95.6% with optimal medical therapy versus 88.9% with TEVAR (p = 0.15). Although there was no difference in mid-term survival, aortic remodeling (defined as true lumen recovery and thoracic false lumen thrombosis) occurred with 91.3% of patients with TEVAR versus 19.4% of those with optimal medical therapy. The question of whether thrombosis of the false lumen in the thoracic aorta has any impact on survival needs further reporting of long term follow up on these patients.

Complicated Type B Dissection

Management of complicated type B dissection remains challenging, as open surgical repair performed under emergent conditions even in experienced centers of excellence is associated with significant morbidity and mortality [21, 24]. Estrera and colleagues reported a mortality of 17% in their series of patients with complicated type B dissection [21]. For this reason, TEVAR is gaining increasing acceptance as an initial treatment for patients with complicated type B dissection [23, 25, 26]. The goal of this therapy is to exclude the primary entry site, obliterate the false lumen, prevent aortic rupture, and relieve lower body malperfusion.

TEVAR in Blunt Traumatic Aortic Injury

Endovascular repair is an effective treatment option in patients who may not be able to undergo open surgical repair safely and may decrease the risk of paraplegia. With the availability of smaller diameter thoracic stent grafts which conform better to the aortic arch in younger patients who are frequently the victims of traumatic aortic injury, TEVAR offers the potential for a durable aortic repair while avoiding the morbidity of a thora-

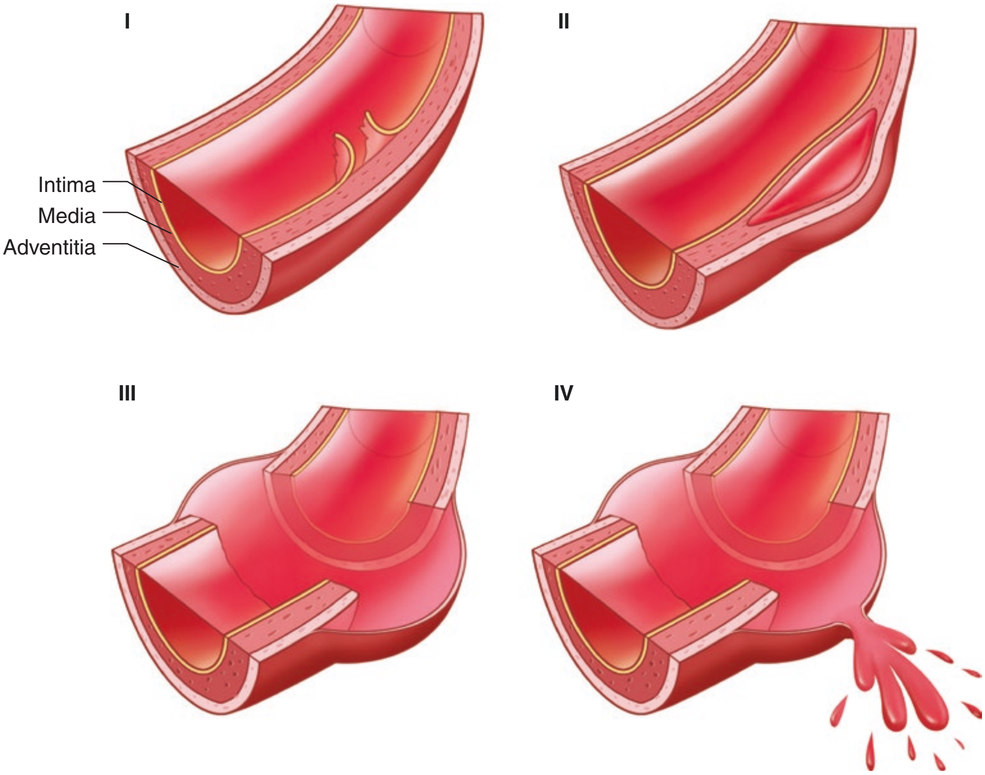

Fig. 59.3 Grading classification of traumatic aortic injury. Grade I—Intimal tear. Grade II—Intramural hematoma. Grade III—Pseudoaneurysm. Grade IV—Rupture

cotomy, aortic cross clamping, and extracorporeal circulation. A classification system for grading and treatment of traumatic aortic injury has been published by Azizzadeh et al., and adopted by the SVS for management of these injuries [13] (Fig. 59.3).

Complications After TEVAR

Endoleaks

Endoleaks (Fig. 59.4) were defined as reporting standards by Chaikof and coworkers [27]. A review of the etiology of endoleaks following TEVAR in 200 patients at the Cleveland Clinic reported an incidence of 19.5% (type I: 7%, type II 8%, type III: 3.5%) with mean follow up of 30 months [28]. The type I and III endoleaks were treated with either secondary endovascular intervention or conservatively. Of the type II endoleaks, glue embolization was used to treat those due to coverage of LSA, the rest were observed. Factors associated with endoleaks were presence of a carotid-LSA bypass, and longer aortic coverage by the stent graft. The authors concluded that secondary intervention is required for most type I and III endoleaks, and conservative treatment is adequate for most type II endoleaks.

Vascular Access Injury

Vascular access injury is a major issue in TEVAR with potentially fatal sequelae. Incidence of injury to access vessels occurs in 1–15% of patients [29–31]. Using large-caliber systems (18-F to 25-F) complications include arterial dissection, rupture, tear or thrombosis, hematoma, pseudoaneurysm, arteriovenous fistula, retroperitoneal bleeding, embolism, and wound infection.

Neurologic Complications

Stroke is among the most feared and devastating complications of endovascular and open repairs of the thoracic aorta. Perioperative stroke has an incidence of 3.5–5.5% with a similar rate in both open and endovascular interventions [32–34]. Most strokes in the anterior circulation likely have an embolic etiology, and posterior circulation strokes are likely ischemic in origin. Over 60% of patients have a dominant left vertebral artery with absent or hypoplastic right vertebral artery, and coverage of the LSA in these circumstances can be associated with significant risk [16].

Retrograde Dissection

Retrograde type A dissection (RAAD) is a rare and catastrophic complication of TEVAR. It is defined as an intimal tear distal to the aortic arch which extends retrograde proximally into the ascending aorta. The incidence has been reported to be between 1.3% and 6.8% [35–38]. RAAD has been attributed to several factors in these series: (1) trauma from the TEVAR procedure (caused by wire manipulation,

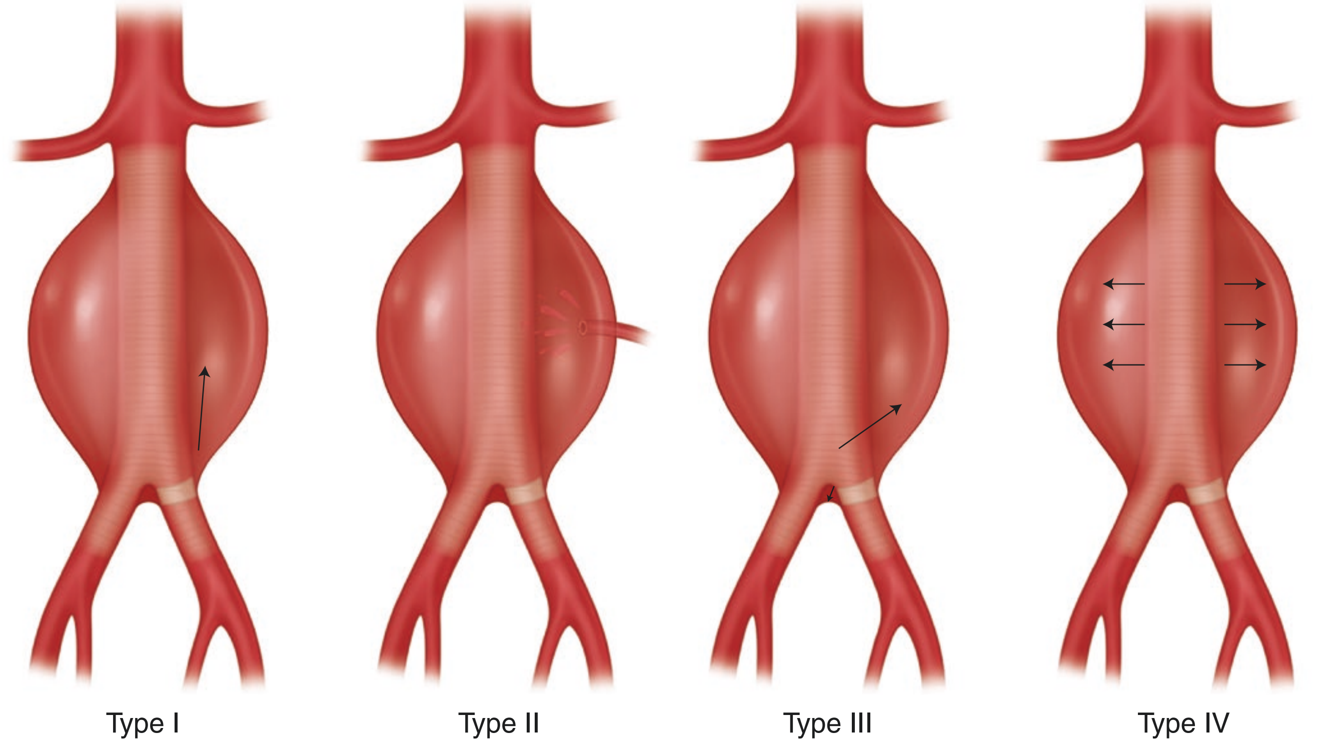

Fig. 59.4 Type I endoleaks are leaks from the proximal (Ia) or distal (Ib) landing zone. Type II endoleaks are not associated with the landing zones or the junction between various stent grafts. Type III endoleaks occur between the components of two or more stent grafts. Type IV endoleaks are caused by graft wall porosity and mainly a problem of first-generation stent graft materials

sheaths/large bore delivery systems, and stent graft balloon dilation); (2) device properties (semi-rigidity and proximal bare spring stent, excessive oversizing >20% causing increased radial force); (3) aortic wall friability (acute and chronic dissection); (4) connective tissue disorders (Marfan syndrome, Ehler Danlos syndrome).

Conclusions

TEVAR is a safe alternative approach to open surgery in properly selected patients for treatment of acute aortic disease with lower early mortality and lower complication rates including paraplegia, especially in high-risk patients. Patient selection is important and TEVAR should be offered to those patients who will benefit the most from this endovascular procedure. Long-term survival, durability, and cost effectiveness remain to be determined. Appropriate recognition and management of TEVAR complications can improve long-term outcomes.

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Neuroprotective Strategies During Aortic Surgery

60

Jee Young Kim, Helen A. Lindsay, and George Djaiani

High Yield Facts

- Spinal cord injury (SCI) occurs when there is an interruption of adequate perfusion to the spinal cord.
- Different strategies can be used to protect spinal cord perfusion as long as the physiological principles of maintaining perfusion pressure are followed.
- Maximising collateral blood flow by supporting mean arterial pressure and reducing cerebrospinal fluid pressure, while prolonging ischemic tolerance and reducing reperfusion injury with hypothermia and pharmacotherapy are the focus of the techniques in preventing SCI.
- Hypothermia and selective cerebral perfusion are the mainstay approaches to prevent stroke or permanent neurological deficits.
- Patients' risk profile, validity of cerebral and somatic monitoring, as well as the importance of institutional familiarity and the role of protocolized care must be prioritized.

Spinal Cord Injury Following Thoracoabdominal Aortic Surgery

Pathophysiology

Spinal cord bloody supply was classically described as two posterolateral spinal arteries and one anterior spinal artery, which is reinforced at multiple levels by segmental arteries originating from the aorta via the intercostal and lumbar arteries [1]. The largest segmental artery ('the artery of Adamkiewicz') arises most commonly from a left intercostal artery, between T9 and T12 in the majority, with significant inter-individual variation. Recently, evidence of a spinal collateral arterial network (SCAN) has evolved, whereby a substantial arterial plexus along the entire length of the spinal cord supports the blood supply with multiple additional inflow vessels [2, 3] (Fig. 60.1).

Complete interruption of the spinal cord blood supply for a sufficient period of time will cause irreversible ischemic necrosis, with the risk significantly higher after 30 min of aortic cross-clamp, and an almost certainty after 60 min [4]. Perfusion may also be permanently suboptimal and become inadequate for viable cord function at a certain "tipping point" [5].

Spinal cord perfusion may be compromised by multiple mechanisms. Blood flow is reduced by direct arterial occlusion with aortic clamp, graft or stent placement. Primary aortic disease processes and emboli can impair anastomotic capacity of the SCAN. Increased cerebrospinal fluid (CSF) pressure or oedema secondary to an ischemia-reperfusion injury can create a 'compartment syndrome' effect. Systemic hypotension or steal phenomenon may further exacerbate marginal perfusion. The potential interconnectedness of these various factors adds complexity, calling for a multimodal approach to prevent spinal cord injury (SCI) (Fig. 60.2).

Identifying Patients at High-Risk

The incidence of SCI ranges from 6–8% with open thoracoabdominal aortic aneurysm (TAA) surgery and 0.8–1.9% with endovascular repair [6]. While endovascular techniques are generally considered to be of lower risk, this is not universal, and increasingly less likely with more complex hybrid techniques, branched and fenestrated stents [7, 8].

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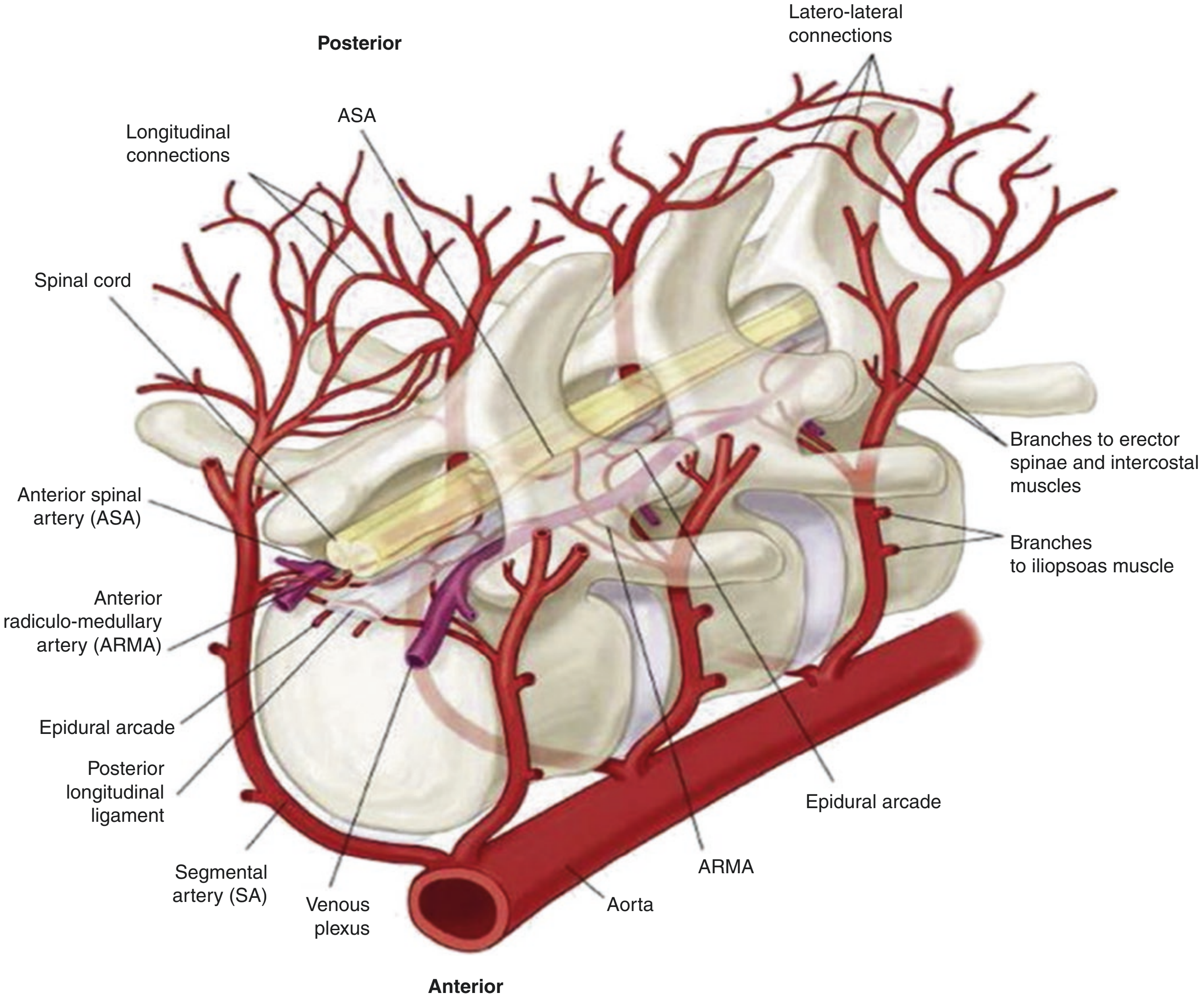
Posterior
Latero-lateral connections
ASA
Longitudinal connections
Spinal cord
Anterior spinal artery (ASA)
Anterior radiculo-medullary artery (ARMA)
Epidural arcade
Posterior longitudinal ligament
Segmental artery (SA)
Venous plexus
Aorta
ARMA
Epidural arcade
Branches to erector spinae and intercostal muscles
Branches to iliopsoas muscle
Anterior

Fig. 60.1 Schematic diagram of the blood supply to the spinal cord (Reproduced with courtesy of Etz et al. [2])

Fig. 60.2 A complex interplay of multiple factors involved in prevention of spinal cord ischemia (*CVP* central venous pressure, *CSFP* cerebrospinal fluid pressure, *HR* heart rate, *MAP* mean arterial pressure, *SCPP* spinal cord perfusion pressure, *SV* stroke volume, *SVR* systemic vascular resistance)

(HR x SV) x SVR

SCPP = MAP − CSFP

The perfusion pressure required to prevent ischaemia.

Qualifying factors:

- Autoregulation / patency of the collateral network
- Metabolic requirements (anaesthetic drugs, hypothermia)
- Time

↑ aortic clamp
↑ cord ischaemia
↓ csf drain

or

CVP

(the higher of the two)

Guidelines emphasize the need to identify "high-risk" patients [9]. The extent of aortic disease, such as Crawford's classification, has long been recognized as an important determinant [10]. Other independent predictors of SCI identified in the literature are extensive, as outlined in Table 60.1, but none have been consistently validated.

Protective Strategies

Despite a range of techniques to prevent SCI, there are still few conclusive recommendations to guide best practice. Heterogeneity in definitions, inclusion/exclusion criteria and therapy combinations between studies are major limi-

Table 60.1 Independent predictors of SCI after endovascular repair and open surgery

Endovascular repair
• Type of repair (I/II/III), aortic coverage length, percentage above the superior mesenteric artery, distal location relative to the celiac artery, total descending thoracic aorta (>6–8 segments), number of stents
• Left subclavian artery covered without revascularization, and occlusion of a single collateral bed
• Previous abdominal aortic aneurysm surgery, simultaneous or previous open infrarenal aortic replacement and concomitant open abdominal aortic surgery
• Dissection and aneurysmal disease
• Duration
• Contrast volume
• Branched/fenestrated grafts
• Age
• Preoperative hypertension
• Chronic renal insufficiency
• Chronic obstructive pulmonary disease
Open surgery
• Extent of disease
• Proximal aortic aneurysm (aneurysm or aortic dissection of the ascending or aortic arch not repaired at the time of surgery)
• Previous thoracic or thoracic aortic aneurysm surgery, with thoracic aneurysm repair being protective in one study
• Aortic rupture
• Total aortic clamp time, which was eliminated as a risk factor on repeat analysis by distal aortic perfusion in a later study by the same group
• Diabetes
• Renal dysfunction

tations. Except for one randomised controlled trial on CSF drainage, the majority of evidence is insufficient, and often conflicting [6, 9].

Cerebrospinal Fluid Drainage

Several case reports and a landmark randomised controlled trial by Coselli et al. [11] validated a potential benefit of CSF drainage, however there are cases of SCI developing despite of prophylactic use of CSF drainage, as well as recovering without it [12]. The recent American College of Cardiology Foundation and European Society of Cardiology guidelines support the use of CSF drainage as a protective strategy in high-risk open and endovascular thoracic aortic repair procedures [6, 9].

One of the most significant complications of CSF drainage is intracranial haemorrhage, with an incidence of 0.45–7.8%. The risks are particularly relevant when the SCI rate is low or predominantly delayed. Some propose the routine use of CSF drainage, while others reserve it as a prophylaxis for selective high-risk cases, or as a rescue therapy in symptomatic patients post-operatively. Unfortunately, there is a paucity in literature to substantiate optimal management standards. Various 'care bundles' are suggested, with consideration of institutional practice being a critical element.

Supporting Spinal Cord Perfusion Pressure (SCPP)

The importance of supporting systemic blood pressure (with mean arterial pressures 80–100 mmHg) and cardiac output to maintain SCPP is widely recognized. Consideration of the patient's pre-operative baseline arterial pressure and withholding antihypertensive agents preoperatively is recommended. Optimization of oxygen delivery with aggressive blood transfusion targets has also been advocated in recent institutional protocols.

The benefits of distal aortic perfusion by cardiopulmonary bypass (CPB), left heart bypass or shunt for open repair of type I–II TAA have been established. However, there is also evidence that non-pulsatile perfusion is not as effective as pulsatile perfusion at the same mean arterial pressure.

Reimplantation of intercostal and lumbar arteries to support collateral flow remains a controversial issue. Historically it has been a popular protective strategy in surgical TAA repair, however there are risks associated with consequent prolongation of the aortic cross-clamp time. Current guidelines suggest a balanced approach with selective reimplantation [9, 13].

The importance of patency of the vessels contributing to the SCAN, and the need for revascularization, is also controversial. Left subclavian artery coverage is an inconsistent risk factor for SCI. Despite this, prophylactic revascularization is often still justified to reduce the risk of stroke or left-arm ischemia.

Staged repair is a relatively new concept based on supporting collateral flow through SCAN remodelling. However, these techniques are still in their early stages, and while feasible, the risk-benefit profile associated with their use requires further evaluation.

Hypothermia

The protective benefits of hypothermia have long been recognized. Various methods including local epidural cooling, profound (<20–22 °C) hypothermia with CPB with or without circulatory arrest, moderate (30–34 °C) hypothermia with partial bypass, and mild permissive hypothermia have been advocated.

However, the association between hypothermia (<34.5 °C) and an increase in post-operative organ dysfunction and mortality in patients undergoing abdominal aortic surgery cautions against widespread use. Currently, moderate systemic hypothermia is considered a reasonable strategy to protect the spinal cord during open surgical repair of the descending thoracic aorta, and epidural irrigation with a hypothermic solution may be considered.

Drugs

The evidence base for pharmacological protective agents remains weak. Intravenous naloxone and intrathecal papaverine have been shown to have a protective benefit in human trials, however the benefits of other drugs including systemic steroids are limited to animal studies.

The 2010 ACCF guidelines recommend consideration of high-dose systemic glucocorticoids, mannitol, intrathecal papaverine, and various anaesthetic agents to suppress spinal metabolism [9].

Preconditioning and Postconditioning

The basis of ischemic preconditioning is a principle of inducing short periods of ischemia that would result in a cascade of events protecting the tissues or organs from subsequent prolonged ischemic events. Various other methods have also been described, including remote ischemic preconditioning, postconditioning, and remote ischemic postconditioning. Despite promising animal studies, these techniques have not made a transition to clinical application in patients undergoing TAA repair, mainly due to unknown optimal timing and duration of preconditioning and postconditioning ischemia, unclear mechanisms by which the potential protection may occur, multifactorial etiology of SCI during surgery, and safety concerns in patients undergoing TAA repair.

A randomized controlled trial led by Etz et al. is testing the hypothesis that pre-operative minimally invasive staged segmental artery coil embolization may reduce paraplegia and mortality in patients undergoing TAA repair (clinicaltrials.gov identifier: NCT03434314). The rationale for this approach lies in findings from recent studies that showed how the deliberate staged occlusion of the segmental arteries to the paraspinous collateral network finally supplying the spinal cord can trigger arterial collateralization, thus stabilizing blood supply from alternative inflow sources and preventing ischemia [14].

Preconditioning with hyperoxia by means of repeated hyperbaric oxygenation (HBO) has shown some success in animal SCI models. HBO treatment is also known to mobilize and increase circulating stem/progenitor cells by stimulating nitric oxide synthesis. However, current clinical practice involves application of HBO only as a rescue therapy if neurologic symptoms persist after TAA repair.

Monitoring

Early detection of inadequate spinal cord perfusion is essential for ensuring implementation of timely interventions before irreversible injury occurs. Early emergence from general anaesthesia and regular neurological assessment of the awake patient following repair are key steps emphasized in post-operative care protocols.

Somatosensory and transcoritcal motor evoked potentials have been used as an indirect assessment tool of spinal cord perfusion in the anaesthetized patient. Consideration for use is recommended in institutions with sufficient resource and experience [9]. This monitoring is limited by delayed ischemia detection and a high rate of false-positive results. Highly sensitive motor-evoked potential monitoring reduces the rate of SCI in the open repair of type I/II TAA, but is limited by resource intensity, the need to restrict neuromuscular blockade and volatile anaesthetic agent use, and theoretical risks of seizure, arrhythmic and neuromuscular complications.

Somatic near-infrared spectroscopy monitoring of the paraspinous muscles has also been used to assess the adequacy of collateral network perfusion, however, further research is required to prove reproducibility.

Brain Injury Following Ascending Aorta and Arch Surgery

Pathophysiology

Multiple mechanisms can cause neurological injury after ascending aorta and arch surgery. Emboli may be dislodged during dissection or vessel manipulation. Global cerebral hypo-perfusion may result when the ischemic time is excessive or the protective strategies are inadequate. Oedema from venous congestion and a local inflammatory response in cerebral tissue are common, from either ischemia-reperfusion injury, or even as a consequence of the protective strategy used.

Identifying Patients at High Risk

The incidences of stroke and permanent neurologic deficits range from 0.8–14%, and temporary neurological dysfunction from 3.3–21.5%, depending on the protective strategies used, and multiple patient and surgical factors.

Independent predictors of neurological dysfunction specific to ascending aorta and arch surgery are outlined in Table 60.2.

Table 60.2 Independent predictors of neurological dysfunction specific to ascending aorta and arch surgery

Stroke
• Age
• Female
• History of cerebrovascular disease, or new preoperative neurological symptoms
• Hypertension
• Diabetes
• Chronic obstructive pulmonary disease
• Previous aortic surgery distal to the left subclavian artery
• Emergency status
• Acute type A dissection
• Operations on the arch or total arch replacement
• Descending aortic aneurysms containing clot/atheroma or general presence of clot/atheroma
• CPB time, duration of cardiac arrest or total cerebral protection time
• History of cerebral infarction or transient ischemic attack (TIA)
• Mitral valve replacement or other concomitant procedures
Temporary neurological dysfunction (delirium, cognitive impairment, confusion)
• Age
• Prior stroke/TIA, history of central neurological event
• eGFR <90 ml/min
• Emergency status
• Acute type A dissection
• Proximal surgery
• Duration of hypothermic circulatory arrest and total cerebral protection time
• Need for coronary artery bypass grafting or other procedures
• Red blood cell transfusion

Protective Strategies

Despite extensive literature, the evidence for neuroprotective strategies is limited. Currently, the 2010 ACCF guidelines recommend (class II) consideration of deep hypothermic cardiac arrest (HCA), and selective anterograde or retrograde cerebral perfusion as 'reasonable' techniques, recognizing institutional experience as an important factor in technique selection [9].

Hypothermia

HCA is the primary brain protection strategy used. Its benefits include simplicity, a bloodless field, and no need for cannula or additional aortic manipulation. Its main limitation is time. The upper safe limit of profound-deep HCA (12–20 °C) is reported to be 25–30 min [15] with >40 min of profound HCA increasing the risk of neurological injury and >65 min increasing the risk of mortality [16].

Potential harms associated with profound and deep hypothermia, including coagulopathy, a pro-inflammatory response and end-organ dysfunction, are largely unsubstantiated in clinical studies. In a meta-analysis comparing deep HCA and moderate HCA with ACP (20.1–28 °C), there was no difference in reoperation for bleeding, renal failure or mortality [17].

Anterograde Cerebral Perfusion (ACP)

Intermittent use of selective cerebral perfusion is the preferred technique for neuroprotection among many surgeons. One of the main benefits of ACP is nutrient support to the brain during a period of circulatory arrest, which has been proven to augment the benefits of deep HCA with circulatory arrest times >30 min [15, 18], others reporting safe ischemic times up to 90 min [19]. However, there are concerns with emboli phenomena and the added CPB time without physiological cerebral circulation.

Unilateral cannulation is simpler with less manipulation of major vessels. Although there is a potential risk of cerebral hemisphere hypoperfusion, a meta-analysis found no difference in the rates of neurological sequelae [20]. Bilateral over unilateral ACP is recommended for circulatory arrest times >30–40 min, however mortality is not necessarily linked to neurological outcome and may be confounded by the inherent risks of having longer, complex surgery [21].

The subclavian-axillary artery is currently the preferred cannulation site, allowing for both CPB and ACP and avoiding a 'sandblast effect' across the atherosclerotic aorta. Other cannulation sites include the ascending aorta, the femoral artery, and the innominate and carotid arteries.

There has been a shift to 'moderate' hypothermia (20.1–28 °C) in order to reduce the rewarming and CPB time, and to limit the risks of hypothermia. While the current evidence supports moderate HCA with ACP as being beneficial to the brain, there is a concern about the inadequate protection of other visceral organs from ischemic injury.

Excessive perfusion results in embolic phenomenon, cerebral oedema with increased intracranial pressure and a rebound increase in metabolism on rewarming, while inadequate perfusion results in inadequate cerebral oxygen metabolism and cellular injury. Suggested guidelines recommend using 40–60 mmHg pressure, 6–10 ml/kg/min flow and a perfusate temperature of 20–28 °C [22, 23].

Retrograde Cerebral Perfusion (RCP)

The benefits of RCP are perceived to be greatest when the risk of embolization is high, as it flushes out debris and air. RCP may also achieve more effective cerebral cooling and wash out ischemic metabolites [24, 25]. However, the risk of cerebral injury due to increased ICP and cerebral oedema needs to be considered [26].

Although the initial recommendations advised a venous pressure of 25 mmHg to avoid brain injury, subsequent evidence suggests higher pressures are needed to open up collapsed cerebral microvasculature. A concept of intermittent pressure augmented-RCP has also been suggested as an alternative strategy [27].

Drugs

Several pharmacological agents are still widely used in clinical practice for cerebral protection despite the lack of evidence to support it. The range of agents used is broad, with thiopentone and steroids being the most common. The theoretical mechanisms for protection are yet to be validated, with little understanding of how this balances with the potential harms of delayed emergence, hypotension and immunosuppression. Recent evidence suggested that prophylactic use of dexmedetomidine for postoperative sedation reduced the rate and duration of postoperative delirium [28].

Topical Head Cooling

The evidence is largely restricted to animal and experimental studies, and generally equivalent or inferior to ACP. The purported benefits relate to preventing rebound warming during cardiac arrest and ensuring uniform cerebral hypothermia.

Acid-Base

pH management during HCA and SCP is controversial, with the clinical evidence in adults being confined to the circumstances of moderate hypothermia for CPB and deep HCA. Studies show either no difference or a benefit for alpha-stat.

Hematocrit

A higher hematocrit (25–30% vs. 10–20%) is associated with improved functional outcomes in animal studies, reduced ICP, improved perfusion pressures and reduced 'luxury' cerebral blood flow.

Monitoring

There is no substantive evidence that the use of any of the cerebral monitoring techniques available reduce the risk of neurological injury. However, they can aid assessment of the adequacy and hemispheric symmetry of cerebral perfusion. A recent study identified that restoration of regional cerebral oxygen desaturation did not result in lower postoperative delirium rates after high-risk cardiac surgery [29].

Although cerebral oximetry monitoring and bilateral radial pressure measurement are most commonly used, a multimodal monitoring strategy may increase the sensitivity of detecting cerebral ischemia.

Bilateral radial artery pressure measurement provides useful information about the perfusion pressure in the contralateral subclavian artery and indirectly measures flow contralateral to the cannulated central artery. Bilateral transcranial doppler can be used to assess the symmetry of middle cerebral artery flow and embolic phenomena but it is limited only to anterior circulation assessment. Auditory and somatosensory multichannel electroencephalography, and jugular venous bulb saturation have also been used to aid detection of intraoperative cerebral ischemia and indicate maximal suppression of cerebral metabolism. However, further research is required to clearly identify their role in the perioperative setting.

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Sinus of Valsalva Aneurysms

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Manish K. Soni and Shahzad G. Raja

High Yield Facts

- The upper limit of normal for sinus diameter for men is 4.0 and 3.6 cm for women, with slight variations when adjusted for body surface area.
- Most cases of sinus of Valsalva aneurysm are congenital.
- It is an uncommon congenital abnormality affecting less than 0.1% of the population.
- The incidence is four times greater in males and more commonly affects people of Asian origin.
- In 65–85% of cases a sinus of Valsalva aneurysm occurs in the right coronary sinus, in 10–30% of cases it presents in the noncoronary sinus, and in <5% of cases it involves the left coronary sinus.
- The average age of rupture is 34 years, with a range of 11–67 years.
- Once rupture has occurred, mean survival is 1–2 years.
- Multiplane transesophageal echocardiography provides conclusive information regarding sinus of Valsalva aneurysms.
- Surgery is the gold standard treatment for ruptured sinus of Valsalva aneurysms.
- Percutaneous closure can be offered in highly selected cases with suitable morphological features.

Introduction

The three bulges of the aortic wall are named the *sinuses of Valsalva*, after the Italian anatomist Antonio Valsalva [1]. Two of the three sinuses host the origin of the coronary arteries and the sinuses are termed accordingly the left, right and non-coronary sinus. They are limited proximally by the attachments of the valve leaflets and distally by the sinotubular junction. At their base, ventricular musculature is partly incorporated. The sinus wall itself is predominantly made up of aortic wall, although it is thinner than the native aorta [2]. The precise function of the sinuses of Valsalva is unclear. There is evidence that the vortices created in the sinuses lead to stress reduction on the aortic leaflets and support coronary flow [3]. Sinus diameter varies by gender. The upper limit of normal for men is 4.0 and 3.6 cm for women, with slight variations when adjusted for body surface area [4]. Enlargement of the sinus beyond these dimensions constitutes an aneurysm. The anatomic positioning of each sinus within the heart is a major determinant of clinical outcome in the case of sinus of Valsalva aneurysm formation and/or rupture. The right sinus lies adjacent to the interventricular septum and the right ventricular parietal bands. The left sinus is proximal to the anterior left ventricular free wall as well as the anterior mitral leaflet. The noncoronary (posterior) sinus rests above the interventricular septum, a portion of the anterior mitral leaflet, and forms a complex with the transverse sinus.

Embryology

Left and right truncoconal swellings develop along the inferior end of the truncus arteriosus during the fifth week of embryogenesis, just before septation of the truncus into anterior pulmonary and posterior aortic channels. After septation, each ventricular outflow tract contains three tubercles, which later form the cusps of the aortic valve and the main pulmonary artery. During the fifth and sixth weeks of embryogenesis, the Valsalva sinuses and aortic valve leaflets begin to form. The right and left main coronary arteries bud simultaneously from their respective developing sinuses. By the ninth week, formation of the aortic valve leaflets and Valsalva sinuses generally is complete [5].

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Pathogenesis

Sinus of Valsalva aneurysms can be either acquired or congenital. Most cases are congenital due to a defect in the aortic wall, more precisely of the continuity between the aortic media and aortic annulus. The essential lesion of a sinus of Valsalva aneurysm is separation of the aortic media of the sinus from the media adjacent to the hinge line of the aortic valve cusp [6]. Connective tissue disorders such as Marfan's syndrome or Ehlers-Danlos syndrome are associated with congenital sinus of Valsalva aneurysms [4, 6]. Other well-recognised associations include bicuspid aortic valve (9%), ventricular septal defects (31%) and aortic regurgitation (44%) [7].

Acquired sinus of Valsalva aneurysms are similarly associated with connective tissue disorders. Infectious etiologies are well-established mechanisms for elastic tissue weakening. Infective endocarditis, syphilis and tuberculosis have each been linked to formation of sinus of Valsalva aneurysms. Other reported causes of acquired sinus of Valsalva aneurysms include chest trauma, vasculitic diseases, and iatrogenic injury during aortic valve replacement [8]. Chronic changes of atherosclerosis and cystic medial necrosis can weaken the intimal layer of vasculature and lead to formation of sinus of Valsalva aneurysms [8].

Epidemiology

It is an uncommon congenital abnormality affecting less than 0.1% of the population [8]. The incidence is four times greater in males and more commonly affects people of Asian origin [9]. In 65–85% of cases a sinus of Valsalva aneurysm occurs in the right coronary sinus, in 10–30% of cases it presents in the noncoronary sinus, and in <5% of cases it involves the left coronary sinus [10]. The average age of rupture is 34 years, with a range of 11–67 years.

Clinical Features

Clinical presentation may be asymptomatic prior to rupture and noted incidentally on imaging. Sinus of Valsalva aneurysms ruptures more frequently into the right ventricle and will typically produce symptoms, with the nature of symptoms depending on the site of rupture. Patients can present with chest pain, acute dyspnoea, palpitations, cardiogenic shock, or sudden death [7]. Once rupture has occurred, mean survival is 1–2 years. Death is usually due to congestive heart failure, but infective endocarditis has been reported as a cause of death in approximately 8% of cases [7]. Ruptures typically occur between 20 and 40 years of age, with notable outliers in infancy or late adulthood [8, 11]. In addition to the size and location, the clinical outcome is predominantly determined by the speed at which a rupture occurs.

An unruptured aneurysm of the sinus of Valsalva may cause right ventricular outflow tract obstruction, infective endocarditis, malignant arrhythmias, myocardial ischemia/infarction due to severe distortion of coronary ostia or compression of the coronary trunks, dilatation of aortic annulus due to anatomical distortion, and cardiac tamponade [12]. However, most nonruptured sinus of Valsalva aneurysms are asymptomatic. Both ruptured and unruptured sinus of Valsalva aneurysms can be complicated by aortic regurgitation, occurring in up to 30–50% of patients [13].

On auscultation, the classic finding is a "loud, superficial sawing murmur prolonged continuously over the first and second heart sounds" [8]. Features of left ventricular hypertrophy and nonspecific ST-T wave changes may be seen on the electrocardiogram (ECG). Chest x-ray may demonstrate a bulging structure in the right caval shadow [13].

Diagnostic Imaging

Multiplane transesophageal echocardiography (TEE) provides conclusive information regarding sinus of Valsalva aneurysms and allows precise identification of structural anomalies and shunt locations for perioperative assessment [14, 15].

Two-dimensional transthoracic echocardiography (TTE) may detect as many as 75% of all patients with sinus of Valsalva aneurysms [16, 17]. Color-flow Doppler imaging is considered the technique of choice for identifying a ruptured sinus of Valsalva aneurysm. However, the use of contrast echocardiography is helpful in delineating the aneurysm and shunt arising from rupture. The presence of a left-to-right shunt can be confirmed by demonstrating a negative contrast image in the right-sided cavities. Usually TEE or magnetic resonance imaging (MRI) is needed to confirm the diagnosis and for perioperative assessment. Features of TTE include the following:

- Generalized single sinus enlargement
- "Wind-sock" extension of sinus from body and/or apex of otherwise normal aortic sinus when ruptured
- Detection of associated defects including ventricular septal defect, bicuspid aortic valve, and aortic insufficiency

Three-dimensional TTE is becoming a valuable tool for prompt bedside diagnosis of sinus of Valsalva aneurysm, especially in ruptured situations. Three-dimensional TEE is useful to determine the precise shape, size, and location of the defect and help guide percutaneous closure device placement [18].

Contrast aortography, MRI and computed tomography (CT) are used as supplemental or confirmatory tests. ECG-

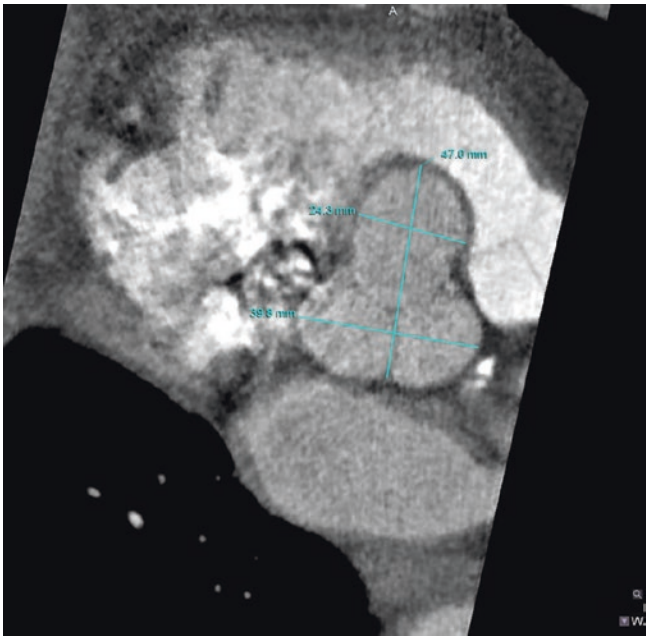

Fig. 61.1 CT scan of a 72 years old male patient showing aneurysm of right sinus of Valsalva. (Cross-sectional view, image courtesy Dr. Tarun Mittal, FRCR)

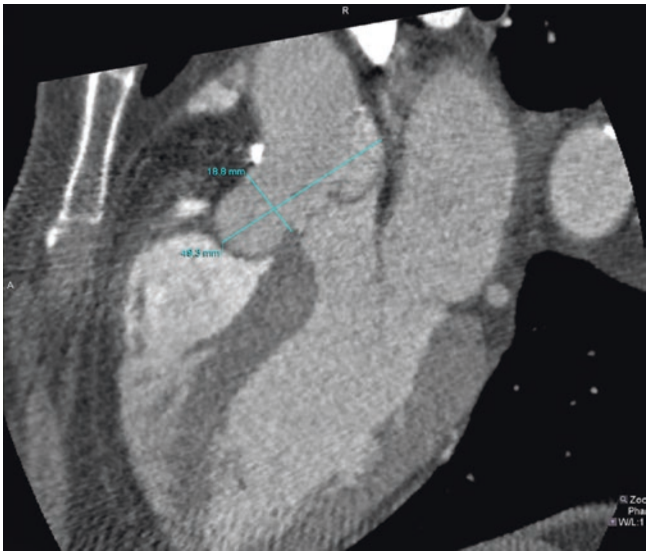

Fig. 61.2 CT scan showing aneurysm of right sinus of Valsalva. (Sagittal view, image courtesy Dr. Tarun Mittal, FRCR)

gated contrast-enhanced multisection CT provides much better spatial resolution of cardiac structures than that attainable with other imaging methods. It also provides detailed anatomic depiction of sinus of Valsalva aneurysms and surrounding cardiac structures (Figs. 61.1, 61.2, and 61.3). The high contrast resolution of CT also makes it possible to delineate an aortocardiac shunt, if present, and to identify a ruptured aneurysm by depicting a jet of contrast material extending from the aneurysm into the adjacent cardiac chamber [19].

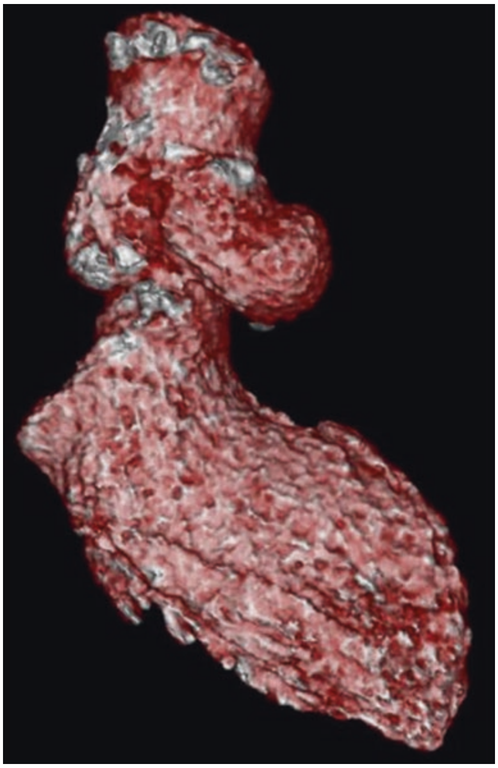

Fig. 61.3 CT scan showing aneurysm of right sinus of Valsalva. (3D reconstruction, image courtesy Dr. Tarun Mittal, FRCR)

Multiplanar MRI with sequences such as balanced steady-state free precession gradient-echo ("bright blood" imaging) and half-Fourier acquisition single-shot turbo spin-echo ("dark blood" imaging) also allow accurate assessment of the origin and size of sinus of Valsalva aneurysms and the status of the surrounding cardiac and mediastinal anatomy [19]. The advantages of performing MRI in the setting of a known or suspected sinus of Valsalva aneurysm include the ability to evaluate the left ventricular hemodynamic pattern, identify aortic regurgitation, and quantify any aortocardiac shunt or turbulent or fistulous blood flow. ECG-gated cine MRI can be performed during a single breath hold and without exposing the patient to ionizing radiation or iodinated contrast material, which is a further fundamental advantage [19].

Management

Medical Management

Medical management usually involves stabilization (e.g., optimizing medications for heart failure syndrome) and perioperative assessment and management [15].

Percutaneous Closure

Surgery is the gold standard treatment for ruptured sinus of Valsalva aneurysms. However, the morphological features of ruptured sinus of Valsalva aneurysm make it amenable to percutaneous closure. The procedure used for closure is practically the same as in the ventricular septal defect (VSD) closure. Since the first report of device closure of ruptured sinus of Valsalva aneurysm in 1994 [20], various case reports and case series have been published [20–33] using patent ductus arteriosus (PDA) occluders, VSD occluders, atrial septal defect (ASD) occluders, Gianturco coils, Rashkind umbrella, etc. (Table 61.1). However, PDA occluders are currently favored [33].

Residual shunt, development of aortic regurgitation or worsening of aortic regurgitation, infective endocarditis, coronary ostial encroachment, and failure to deploy are important complications of device closure in ruptured sinus of Valslava aneurysms described in the literature so far [33].

Percutaneous closure of ruptured sinus of Valsalva aneurysms is evolving. Relative paucity of cases remains the major limitation, apart from the difficulty in closing defects >12 mm with currently available devices [33]. However, complications reported in the literature due to percutaneous closure are scanty, and with the evident good long-term outcome, percutaneous closure may be regarded as a safe alternative to surgery for carefully selected cases in expert hands.

Table 61.1 Published experience of percutaneous closure of ruptured sinus of Valsalva aneurysm

Author	Year of publication	No. of cases	Device used
Cullen et al. [20]	1994	1	Rashkind umbrella
Rao et al. [21]	2003	1	Gianturco coil
Arora et al. [22]	2004	8	ADO (5), ASO (1), and Rashkind umbrella (2)
Abidin et al. [23]	2005	1	ASO
Chang et al. [24]	2006	4	ADO (3) and Gianturco coil (1)
Zhao et al. [25]	2008	10	ADO
Sen et al. [26]	2009	8	Heart PDA
Szkutnik et al. [27]	2009	6	ADO (5)ASO (1)
Kerkar et al. [28]	2010	20	ADO
Guan et al. [29]	2013	10	PDA (8) and VSD (2)
Radhakrishnan et al. [30]	2013	13	ADO
Tong et al. [31]	2014	13	PDA
Rittger et al. [32]	2015	1	AVP II
Sinha et al. [33]	2015	7	PDA

ADO amplatz duct occluder, *ASO* amplatz septal occluder, *AVP II* amplatz vascular plug II, *PDA* patent ductus arteriosus occluder, *VSD* ventricular septal occluder

Surgical Management

Surgical intervention is recommended for a ruptured sinus of Valsalva aneurysm and/or a sinus of Valsalva aneurysm with associated intracardiac abnormalities such as ventricular septal defect or significant aortic valve regurgitation. An unruptured but symptomatic or enlarging sinus of Valsalva aneurysm should also be considered for surgical repair. Although specific guidelines for repair of a sinus of Valsalva aneurysm are yet to be established, it is generally accepted to follow repair guidelines for aortic root aneurysm. According to the 2010 American Guidelines on Thoracic Aortic Disease, surgical repair should be considered in those with aneurysms >5.5 cm, >5 cm in those with bicuspid valves, >4.5 cm in the setting of connective tissue disease, or a growth rate of >0.5 cm/year [34].

Since the first successful surgical repair of a sinus of Valsalva aneurysm by Lillehei in 1957 [35], different surgical approaches and repair techniques have been described. All surgical repairs are done with cardiopulmonary bypass and cardioplegic arrest. There are three main operative approaches: (1) through the aortic root via an aortotomy, (2) through the cardiac chamber in which the aneurysm has ruptured, or (3) a dual approach through both an aortotomy and an incision into the involved cardiac chamber. The choice of approach is determined by the presence of aortic valvular pathology such as aortic regurgitation, the size of the aneurysm, the presence of concomitant cardiac anomaly such as a VSD, and the cardiac chamber involved. There are two main closure techniques: primary closure and patch closure. Primary closure has been routinely used for the repair of small sinus of Valsalva aneurysms. Patch closure is preferred for repair of larger sinus of Valsalva aneurysms, as primary closure in those cases may distort the aortic sinus resulting in aortic valve incompetence, or may cause excessive tissue tension in the repair site resulting in delayed recurrent rupture [8].

With an operative mortality rate of 1.9–3.6% and actual survival rates of close to 90% at 15 years [36–38], surgical repair of sinus of Valsalva aneurysms can be performed with acceptably low mortality and good long-term outcome. Early surgical intervention should therefore be considered prior to worsening symptoms and the development of complications.

Conclusion

Sinus of Valsalva aneurysm is a rare but potentially serious condition. Proper and timely diagnosis is crucial to the outcome of patients, particularly when rupture has occurred. Echocardiography is often the initial diagnostic imaging modality of choice as it is ubiquitous, relatively inexpensive, and without need for radiation or iodinated contrast administration. Rupture usually manifests as a sudden onset of chest pain and acute heart failure in most of the cases. Death usually occurs within 1 year of untreated ruptured sinus of Valsalva aneurysm. Percutaneous treatment is emerging. However, surgery remains the main stay of treatment for this potentially life threatening condition.

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Elephant Trunk Procedures

62

Suyog A. Mokashi and Lars G. Svensson

High Yield Facts

- The elephant trunk is the gold standard surgical procedure for aortic arch disease.
- A tube graft floating in the descending aorta (while replacing the ascending aorta and arch) and inverting the graft within itself were both critically important for the development of the elephant trunk procedure used today.
- Svensson's elephant trunk classification includes location of the anastomoses, captures hybrid repairs and improved brain protection methods.
- Appropriate patient selection and preoperative assessment are frequently the major determinants in successful surgery.
- Cardiopulmonary bypass inflow should be the right subclavian/axillary artery with an attached 8-mm side graft.
- Circulatory arrest should involve cooling to a nasopharyngeal temperature of 20 °C, with antegrade brain perfusion.
- Dissecting close to the aortic arch, without mobilizing the head vessels, preserves the vagus and recurrent laryngeal nerves.
- The distal elephant trunk should be kept approximately 10–15 cm in length.
- For the second stage elephant trunk, an aortotomy beyond the left subclavian artery precludes significant blood loss as the elephant trunk is surrounded by thrombus to identify the graft.
- For the frozen elephant trunk, apposition of the stent graft and aorta is essential to prevent migration and endoleaks.
- Lifelong postoperative surveillance is necessary after aortic arch surgery.

Introduction

The surgical treatment for extensive aortic diseases involving the arch can be a complicated enterprise. In fact, most aneurysms in this area are synonymous with disease of the adjacent ascending or descending thoracic aorta. The paradigm shift toward current surgical management occurred with the so-called elephant trunk procedure (ET) that has evolved as the primary treatment for combined diseases of the aortic arch and distal aorta [1–6]. The ability to simplify the second stage procedure, required after the aortic arch has been repaired, was the most important innovation that allowed for this paradigm shift. More recently, the emergence of the hybrid arch has been appreciated for treating patients with extensively diseased thoracic aortas [1–6].

Evolution of the Elephant Trunk

The roots of aortic arch surgery extend well into Houston. The first scholarly treatise on thoracoabominal aneurysm repair—28 patients with an impressive survival rate of 92%—was by Crawford in 1974 [2]. In 1981, Crawford and Saleh, described working entirely within the aneurysm and wrapping the graft with aneurysm wall: the inclusion technique [3, 4]. A few years later, Borst devised a method of leaving a piece of tube graft floating in the descending aorta while repairing the ascending aorta and aortic arch; this served to replace the descending aorta during the second stage [5]. During the next decade, it became evident that tension exerted on the wall by the needle during suturing at a difficult angle sometimes resulted in tearing of the aortic wall [1]. The ET was refined by Svensson to invert the graft within itself; he sewed the doubled-over edge into position beyond the left

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subclavian artery, and then withdrew the inner inverted tube for the arch repair [1, 6]. It was Svensson's modification that eased the procedure and resulted in a better than 90% survival rate for the first and the second stage repairs [1].

Increasingly, more modern techniques have centered on less invasive therapies. This is evident, in particular, with hybrid procedures combining open surgical repair with endovascular stent grafting. To that end, endovascular stent grafting of the descending aorta is now more commonly used compared to conventional open techniques. For involvement of the arch, combined approaches including the frozen elephant trunk (FET) may be utilized as an adjunct to the standard arch replacement [7–10]. A stent graft is delivered in the descending aorta at the time of arch surgery; this obviates the need for further open surgery.

Classification of Elephant Trunk Repairs

Our group has devised a method of classifying elephant trunk procedures used to grade the location of the anastomoses, which captures hybrid repairs (Fig. 62.1) and also improved brain protection methods [11, 12].

Preoperative Evaluation

Despite advances in aortic arch surgery, the best treatment plan still depends initially on general patient factors. Appropriate attention must be paid to preoperative assessment and planning in establishing whether a patient is a suitable candidate for surgery. Documentation of thoracic aneurysm with computed tomographic angiography (CTA) is a critical part of the diagnostic imaging sequence. This delineates the aneurysm size, arterial tortuosity, arterial wall calcification, and intravascular thrombus. Our preference is to process image CT data to create three-dimensional reconstructions. Formerly the "gold standard," conventional aortography is seldom required in contemporary practice.

Routine measurement of laboratory work (serum chemistries, hematologic profile, and coagulation studies), pulmonary function tests, 24-h Holter examination, brain MRI or CT, and carotid duplex studies should be performed. Pulmonary function testing may help to uncover and identify whether patients will tolerate an open second-stage procedure, if needed. Transthoracic echocardiography and left heart catherization is routinely conducted.

Anesthetic Management

Optimal outcomes extend beyond the purview of the surgeon. Anesthesia for aortic arch surgery is complex and depends on close communication between the anesthesiologist and the surgeon before, during, and after the operation. Bilateral brachial arterial lines and a femoral arterial line for simultaneous monitoring of brain and systemic perfusion pressures, central venous access with pulmonary artery catheters for monitoring cardiodynamics (cardiac index and filling pressures) and transesophageal echocardiography to evaluate aortic valve function and endoleak detection are of paramount importance [13]. Bladder and nasopharyngeal temperature are monitored during hypothermia and subsequent rewarming [13]. Given surgical blood loss can be considerable, aggressive blood component replacement with packed red blood cells and clotting factors must be immediately available [13]. We no longer use EEG monitoring.

Cardiopulmonary Perfusion and Brain Protection

Our understanding of the complex mechanisms of cell death from ischemic injury has led to the introduction of myriad neuroprotective measures during aortic arch surgery [12]. Intraoperative events, such as systemic hypotension and excessive blood loss causing a decrease in brain perfusion, can precipitate ischemic changes. Several techniques maybe used in an attempt to provide brain protection and simultaneous facilitation of a controlled surgical field [12].

Our preference for cardiopulmonary bypass inflow is the right subclavian/axillary artery with an attached 8-mm side graft. The portion of the artery proximal to the lateral edge of the first rib allows perfusion of the vessel, both proximally and distally, and greater flow rates [12]. Once the patient is systemically heparinized, the graft is carefully de-aired and connected to a three-eighths-inch to quarter-inch perfusion connector that is then connected to the arterial line of the cardiopulmonary bypass machine [12]. In patients who have had an aortic dissection extending in the subclavian artery, the vessel should be avoided. The femoral artery should instead be used and the right femoral artery is preferable. Care must be taken to ascertain that there is no atheroma present in the arterial system that may potentially embolize with retrograde pumping through the femoral artery up to the brain [12].

Hypothermia ameliorates the primary and secondary mechanisms of ischemic injury. Our preference during circulatory arrest is cooling to a nasopharyngeal temperature of 20 °C, with antegrade brain perfusion as a useful adjunct. Although moderate hypothermia avoids long cooling and rewarming periods, decreases cardiopulmonary bypass times, and avoids coagulopathy; should the circulatory arrest times exceed 40 min it can be a major risk factor for systemic and spinal ischemic injury [12]. Moreover, we often use antegrade brain perfusion, if not throughout the period of circulatory arrest for total arches, at least at intermittent intervals when convenient from the point of view of visualizing the field and suturing based on our prospective randomized trial of brain protection [12].

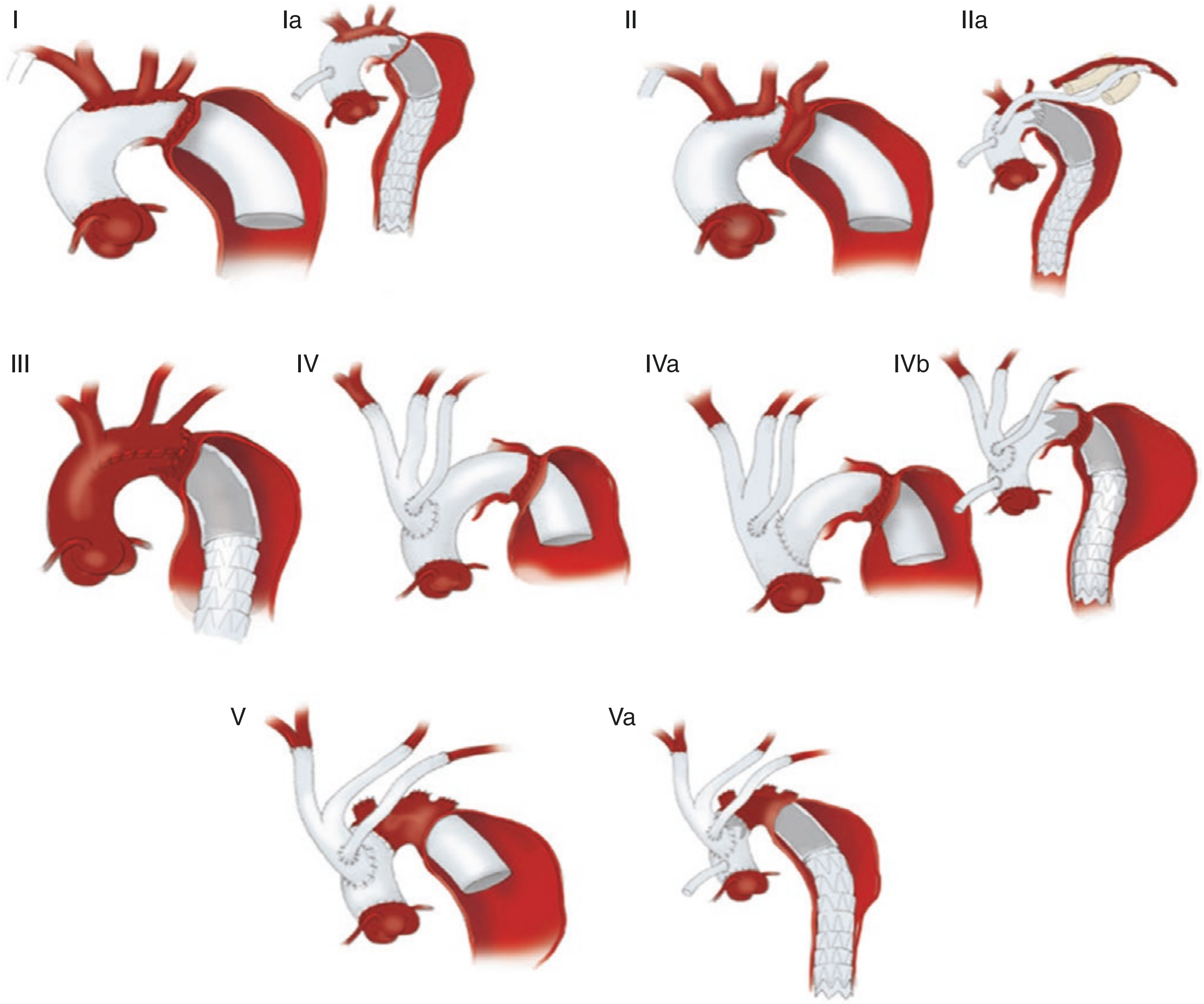

Fig. 62.1 Classification of anastomotic sites of elephant trunk for repair of thoracic aorta disease. Type I—Classic elephant trunk with an ascending tube graft with total arch replacement and elephant trunk anastomosis in classic position distal to left subclavian artery (LSCA). If repair with stent graft, Type Ia. Type II—Ascending aorta tube graft with arch replacement and elephant trunk anastomosis proximal to LSCA. If subsequent thoracic stent graft with proximal landing zone covering LSCA and a descending-to-LSCA bypass, Type IIa. Type III—Elephant trunk placed into large descending aortic aneurysm used as a landing zone for distal thoracic stent graft. Type IV—Ascending aorta tube graft with classic elephant trunk anastomosis into distal thoracic aneurysm with branched graft for total arch replacement. If ascending branched graft for replacement of ascending aorta and arch, with end-to-side elephant trunk in classic position, Type IVa. Subsequent thoracic stent graft in type IV repair, Type IVb. Type V—Ascending aorta tube graft with elephant trunk anastomosis proximal to brachiocephalic artery and a branched graft for total arch replacement. If Type V repair configuration with thoracic stent graft in distal aneurysm, Type Va [11]. (Image from Modifications, classification, and outcomes of elephant-trunk procedures. Ann Thorac Surg 2013;96:548–558)

Operative Technique: First Stage Conventional Elephant Trunk

Typically, an 8-mm side graft is attached to the right subclavian or axillary artery. This is especially well suited for arterial inflow during cardiopulmonary bypass, but also affords selective antegrade brain perfusion during circulatory arrest. After median sternotomy and pericardiotomy are made, a multistage cannula is placed in the right atrium for venous cannulation. The patient is placed on cardiopulmonary bypass, which is followed by cooling. The aortic arch is exposed, beginning at the left anterior lateral surface to approximately 2 cm beyond the left subclavian artery [1]. Care should be taken to preserve the vagus and recurrent laryngeal nerves. This is best performed by maintaining the plane of dissection close to the aorta and not dissecting or mobilizing the head vessels. Preparation of the elephant trunk and inverting the graft can occur in parallel while cooling. Depending on size, a 23- to 30-mm woven Dacron tubular prosthesis is selected [1]. A stay suture with hemostat is placed on the proximal end of the tube graft and both are then inverted so that the proximal part is invaginated into the more

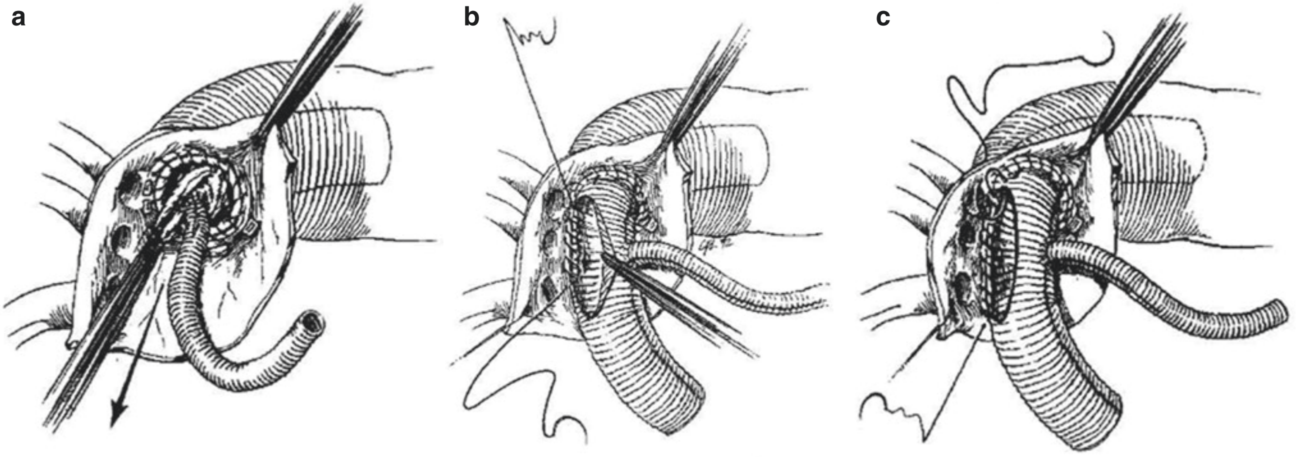

Fig. 62.2 (**a**) Removal of the inner tube graft and side arm from the distal aorta. (**b**, **c**) Anastomosis of the arch vessels to the opening in the aortic graft [1]. We no longer use the side graft to establish antegrade perfusion but instead use the subclavian inflow [11, 12]. (Image from Rationale and technique for replacement of the ascending aorta, arch, and distal aorta using a modified elephant trunk procedure. J Card Surg 1992;7:301–312)

distal tubular graft [1]. The distal elephant trunk should be kept approximately 10–15 cm in length. In addition, we place two large clips and a pacing wire loop on the end that can be used for exacting traction on a crumpled elephant trunk graft.

When 20 °C nasopharyngeal temperature is reached, circulatory arrest begins. At this point, cardiopulmonary bypass is stopped and the patient is placed in a steep Trendelenburg position to prevent air accumulating in the arch vessels [1, 12]. Carbon dioxide is also run into the field at 10 L/min [12]. The aneurysm is then entered in the mid-ascending aorta, opened along the arch, and, distally, to an anterior lateral position above the subclavian artery origin. If there is a chronic aortic dissection, the septum is excised as far as possible in the descending thoracic aorta, so that true and false lumens are perfused distally by the elephant trunk [1, 12]. Perfusion of either the true or false lumen alone may result in paraplegia or renal failure. The inverted graft is placed in the descending aorta and an anastomosis between the inverted edge of the elephant trunk graft and aorta just beyond the subclavian artery is then performed (Fig. 62.2) [1, 12].

Alternatively the anastomosis is done more proximally as needed [11]. After completion of the anastomosis, the stay suture is gently tugged upon to remove the inverted proximal graft from the distal elephant trunk and the arch vessels are then ready to be re-anastomosed (Fig. 62.2) [1, 11, 12]. By withdrawing the inverted graft from inside the elephant trunk, the anastomosis is tightened and hemostasis is improved. Next, an opening is made in the graft opposite the arch vessels and reattachment of the arch vessels is performed (Fig. 62.2) [1, 11, 12]. The graft is flushed, clamped and checked for hemostasis. Cardiopulmonary bypass is restored and warming commenced. Finally, the proximal ascending aorta anastomosis and/or aortic valve or root procedure is completed.

Operative Technique: Second Stage Conventional Elephant Trunk

Six to twelve weeks after the first stage, the second stage of the elephant trunk procedure is performed [1, 11, 12]. Positioning is best achieved by placing the patient in right lateral decubitus with the pelvis tilted to approximately 60° of flexion [1]. A surgical beanbag positioner is used to further secure the patient in this position. The incision is placed according to the planned extent of the aneurysm, which can be carried onto the abdomen. An aneurysm confined to the descending thoracic aorta requires a posterior lateral thoracotomy through the left fourth or fifth interspace [1, 12]. For a thoracoabdominal aneurysm, a retroperitoneal approach usually via the left sixth interspace allows for superior exposure. The retroperitoneal approach allows the abdominal contents to fall away from the surgical field and also eliminates the difficulties posed by entering the abdomen. Typically, the diaphragm can be preserved for aneurysms above the celiac artery and divided (including left crus) for aneurysms below the superior mesenteric artery [1]. The external oblique, internal oblique, and transversus abdominis muscles are sequentially divided. The peritoneal and retroperitoneal contents are swept anteriomedially to expose the aorta. Every attempt should be made not to violate the peritoneum.

The aortotomy and anastomoses are now performed. The anterior lateral aorta is longitudinally entered at the site of the previous distal elephant trunk anastomosis; a point immediately beyond the left subclavian artery [1]. The distal elephant trunk should be surrounded by thrombus to identify the graft. Strict maintenance of this plane precludes significant blood loss [1]. Once the graft is identified, it is encircled and clamped (Fig. 62.3). Next, a view

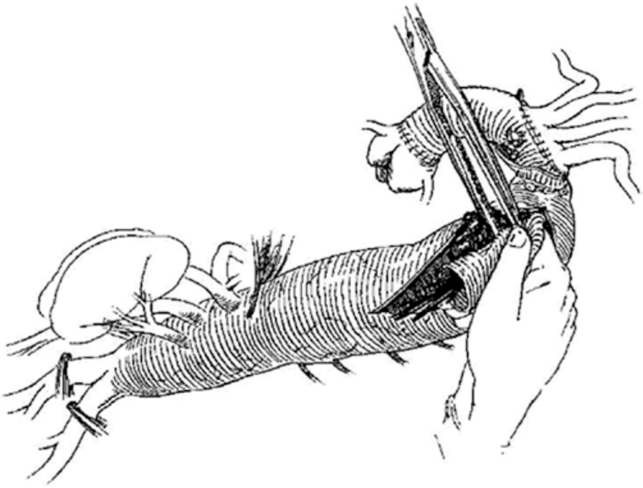

Fig. 62.3 Clamping of the elephant trunk in the descending thoracic aorta [1]. (Image from Rationale and technique for replacement of the ascending aorta, arch, and distal aorta using a modified elephant trunk procedure. J Card Surg 1992;7:301–312)

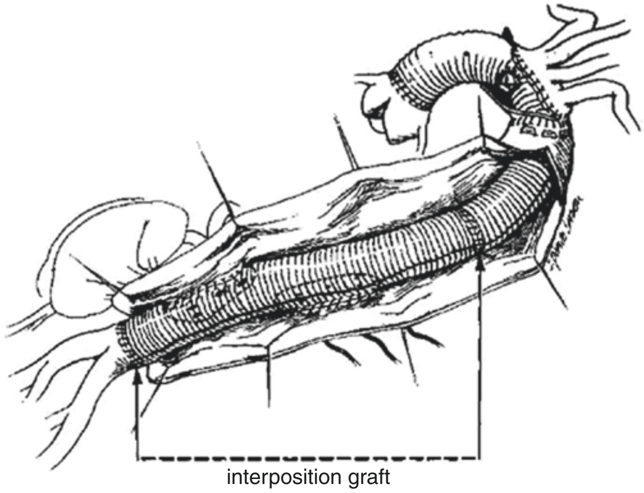

Fig. 62.4 Insertion of the interposition aortic graft, with reattachment of the intercostal arteries and visceral vessels [1]. (Image from Rationale and technique for replacement of the ascending aorta, arch, and distal aorta using a modified elephant trunk procedure. J Card Surg 1992;7:301–312)

of the intercostal arteries is now possible. Whenever possible, the goal is to reattach segmental intercostal arteries from T8 to include all the lumbar arteries; this enables reestablishment of blood flow to the spinal cord by the artery of Adamkiewicz and higher thoracic spinal radicular arteries [1, 11]. Finally, the proximal anastomosis is performed, followed by the distal anastomosis to the circumferentially transected aorta. If the elephant trunk is insufficient to bridge the gap, an interposition graft will be needed for the distal aortic anastomosis (Fig. 62.4) [1].

Operative Technique: Frozen Elephant Trunk

The procedure begins similar to the conventional elephant trunk, with an 8-mm right subclavian/axillary side graft and a multistage cannula in the right atrium. Cardiopulmonary bypass and systemic cooling are initiated. The proximal arch and arch branch vessels are then individually dissected, with care taken to preserve the vagus and recurrent laryngeal nerves [1, 11]. The innominate and left common carotid arteries are snared and selective antegrade brain perfusion is commenced [14, 15]. The aorta is then transected obliquely in a hemiarch fashion, starting from the base of the innominate artery to the underside of the aortic arch [14, 15].

Preferably, the left subclavian artery is cannulated with a 9-Fr occlusion balloon to avoid steal from the left vertebral system [14, 15]. The stent-graft is deployed antegrade into the true lumen and positioned across the aortic arch [14, 15]. Alternatively, at times the anatomy may be complicated and a transfemoral wire can be particularly useful as an adjunct to deliver the stent-graft. The graft is positioned to cover the left subclavian artery ostia and secured to the lesser curve of the aortic arch, to prevent migration [14, 15]. Next, a handheld cautery is used to create an opening in the stent-graft at the level of the left subclavian artery [14, 15]. A bridging branch stent-graft (2.5 cm length) is directly positioned through the main stent-graft and deployed into the left subclavian artery. The branch stent-graft opening should be expanded by direct manipulation with a clamp and gently molded with the soft, conformable 9-Fr occlusion balloon [14, 15]. Next, the main stent-graft is directly sutured to the transected aortic wall; care must be exercised to ensure apposition of the stent graft and aorta to prevent migration and endoleaks. A surgical hemigraft, ideally the diameter of the sinotubular junction, is used for the open distal anastomosis—incorporating the hemigraft, transected aorta and stent-graft [14, 15]. The innominate and left carotid flows are resumed, the graft deaired and cardiopulmonary bypass is re-instituted. Finally, the valve and root are addressed and proximal aortic reconstruction with the proximal end of the surgical graft is completed (Fig. 62.5) [14, 15].

Postoperative Surveillance

Lifelong surveillance of patients and their aortas is recommended. Follow-up must commence shortly after discharge and eventually become an annual event. The recognized ractice is to obtain a postoperative CTA that includes the chest, as well as the abdomen and pelvis before discharge, 3 months postoperatively and then annually [11, 14, 15]. Postoperative CTA surveillance allows for the detection of endoleaks, aneurysm sac expansion, stent fracture, and material fatigue.

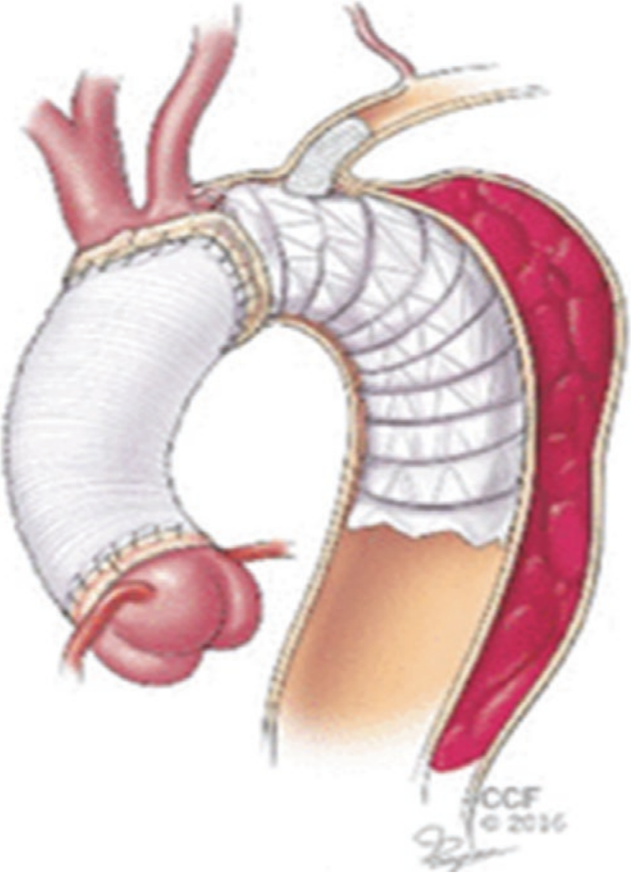

Fig. 62.5 Cleveland Clinic Frozen Elephant Trunk with direct bridging arch branch stent-grafting—Branched Single Anastomosis Frozen Elephant trunk Repair (B-SAFER) [14, 15]. (Image from Evolution of Simplified Frozen Elephant Trunk Repair for Acute DeBakey Type I Dissection: Midterm Outcomes. Ann Thorac Surg 2018;105:749–755)

Outcomes

As endovascular devices have become more versatile and outcomes more durable, the aneurysms that remain for open repair have become increasingly complex. We published our series of 526 unselected elephant trunk procedures with superb outcomes [11]. The survival rate for the first operation was 92% and the overall stroke rate was 8% [11]. Furthermore, in our prospective randomized trial of brain protection during total arch replacement, the clinical stroke rate was 0.8% and the mortality rate 0.8%, including most of them having elephant trunk procedures. The 1-, 4-, and 8-year risk of death before second-stage elephant trunk was 16%, 22%, and 27%, respectively [11].

We recently reported our series of 72 patients undergoing frozen elephant trunk for an acute DeBakey type I dissection [16]. Operative mortality was reported as 4.2%. Survival was 92% at 6 months, 92% at 1 year, 89% at 3 years, and 80% at 5 years [16]. Moreover, freedom from re-intervention was 93% at 6 postoperative months, 87% at 1 year, 77% at 3 years, and 72% at 5 years [16].

Conclusion

The elephant trunk procedure remains the mainstay of management for extensive aortic arch disease. The elephant trunk procedure has resulted in a remarkably safe and effective repair, with a good long-term prognosis.

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Porcelain Ascending Aorta

63

Yigal Abramowitz and Raj R. Makkar

High Yield Facts

- The term “porcelain aorta (PA)” has been used to address extensive circumferential or near circumferential calcification of the thoracic aorta such that it precludes safe cross-clamping and/or entry into the ascending aorta.
- CT scan is the most effective, noninvasive modality for the diagnosis of aortic calcification and PA.
- The two independent processes that lead to the formation of aortic calcification are atherosclerosis that occurs as a result of inflammatory response involving the tunica intima and calcification of mainly the medial layer of the aorta in the absence of atheroma.
- PA is usually an incidental finding in patients being evaluated for cardiovascular or pulmonary diseases.
- The prevalence of PA was found to be 7.5% among patients evaluated for aortic stenosis (AS), between 1.2% and 13.6% among patients undergoing valvular or coronary revascularization surgeries, and between 5% and 33% among patients undergoing transcatheter aortic valve replacement (TAVR).
- There is growing evidence that identification of ascending aortic and/or aortic arch calcification can also be related independently to higher risk of cardiovascular events and mortality.
- An important clinical implication of PA is an increased risk of stroke during cardiac surgery due to embolization of atheromatous material caused by manipulation of the ascending aorta.
- Patients with PA undergoing conventional cardiac surgery require procedural modifications to attenuate neuroembolic risk and safe aortic entry and closure.
- TAVR is a safe and effective option for patients with severe symptomatic AS and PA.

Introduction

Porcelain ascending aorta (PA) is extensive calcification of the ascending aorta and/or aortic arch which can be completely or near completely circumferential [1]. The prevalence of this entity is rare in the general population, but it has an increasing incidence in older patients and in patients with coronary artery disease or aortic stenosis (AS) [2, 3]. The clinical relevance is based on the fact that it can complicate surgical aortic valve replacement (SAVR) for the treatment of severe AS by preventing safe access via the ascending aorta. PA is associated with increased morbidity and mortality, especially as a result of increased perioperative stroke risk [4, 5]. Transcatheter aortic valve replacement (TAVR) has emerged as a less invasive and feasible treatment option in patients at high risk for conventional SAVR [6]. In some series, approximately 20% (5–33%) of the patients undergoing TAVR are diagnosed with PA [7]. Inconsistencies in definition and utilization of different diagnostic modalities contribute to this wide range of PA prevalence.

Definition and Diagnosis

The term “porcelain aorta” has been used to address extensive circumferential or near circumferential calcification of the thoracic aorta such that it precludes safe cross-clamping

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and/or entry to the ascending aorta. However, there is no clear description or definition employed and thus cardiac surgeons and cardiologists use this term inconsistently [1]. In the 1980s Coselli and Crawford [8] initially described two patients using the term "porcelain aorta" for heavy calcification of the ascending aorta and aortic arch as diagnosed by chest radiography or palpation intraoperatively. Svensson et al. [9] defined PA as calcification of the ascending aorta and aortic arch involving predominantly the aortic media. Leyh et al. analyzed 1861 patients undergoing coronary artery bypass grafting (CABG) and found 23 patients (1.2%) with PA defined as circumferential severe calcification of the entire ascending aorta and proximal aortic arch [10]. Several additional case reports and small case series of patients with PA undergoing cardiac surgery were published. The exact definition of PA varied between authors, but the common denominator that best describes the clinical problem is aortic calcification that interferes with aortic cannulation, aortic clamping, aortotomy and/or central coronary bypass anastomosis, necessitating modification of the surgical technique to avoid complications [11].

There are diverse modalities used for the diagnosis of PA and a lack of clear definition regarding how PA should be diagnosed. Not uncommonly, PA is recognized by manual palpation performed after sternotomy and exposure of the aorta at the time of cardiac surgery [12]. Occasionally, a chest X-ray might reveal calcific outline of the ascending aorta and/or arch (Fig. 63.1). Fluoroscopy during coronary angiography can also show diffuse, generalized calcification of the walls of the ascending aorta suggesting the diagnosis of PA (Fig. 63.2), but it is not an accurate modality for the assessment of the extent of aortic calcification [13]. PA may also be an incidental finding during echocardiography (Fig. 63.3). The most sensitive technique for detecting ascending aortic atheroma and calcification *during* open heart surgery is the epiaortic echocardiographic scanning of the aorta in conjunction with manual palpation [2, 13, 14]. Electron-beam computed tomography (EBCT) and multislice (spiral) CT are effective, noninvasive techniques for cardiac, coronary and aortic calcification imaging pre-procedurally [13, 15, 16]. It is used to accurately evaluate the extent of ascending aorta and aortic arch calcification thus differentiating between PA (circumferential) and less extensive aortic calcification as well as the

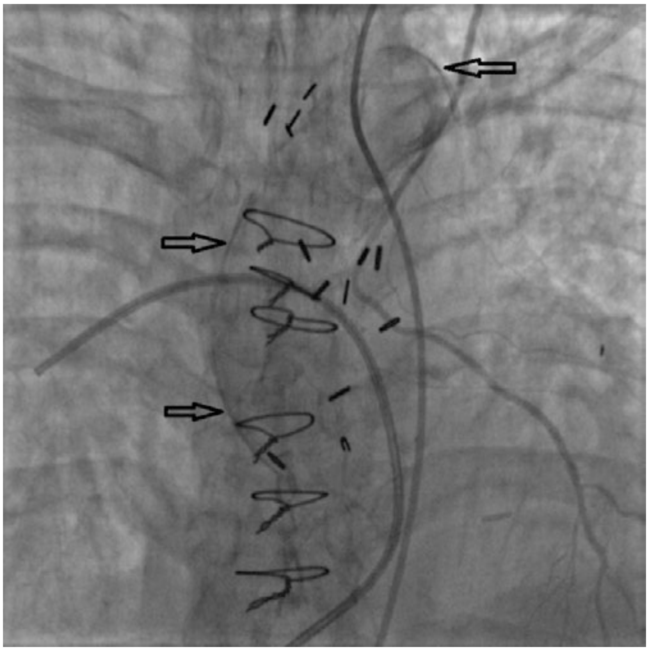

Fig. 63.2 Angiography during selective injection to the left internal mammary artery graft showing heavily calcified ascending aorta and aortic arch (black arrows)

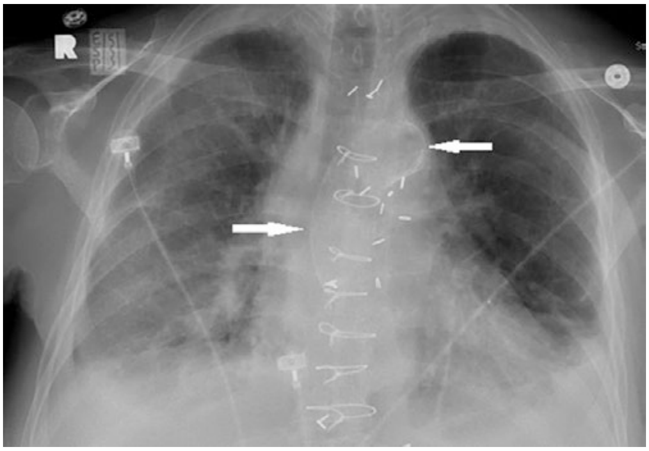

Fig. 63.1 Chest X-ray showing calcified ascending aorta and aortic arch (white arrows)

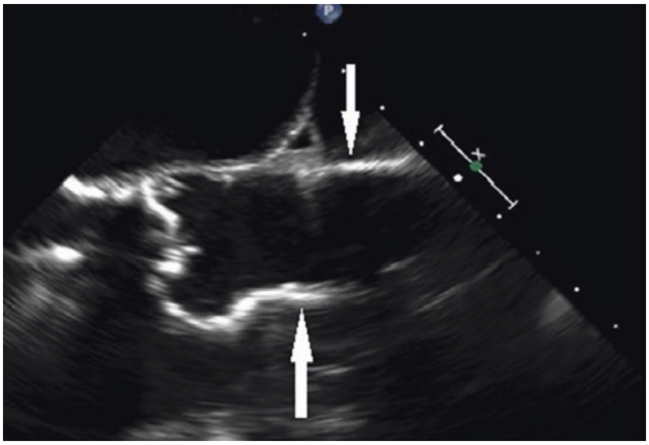

Fig. 63.3 Transesophageal echocardiogram showing calcification of the aortic valve and ascending aorta (white arrows)

exact location in the ascending aorta and arch (Figs. 63.4 and 63.5) [2, 5, 13, 17].

Currently, in the TAVR era, the term "porcelain aorta" is frequently used. It became an important factor for patient selection and sometimes serves as the primary indication for TAVR approach even in intermediate risk patients [18]. The PARTNER (Placement of Aortic Transcatheter Valves) trial, defined PA as near or complete circumferential calcification of the ascending aorta and/or aortic arch [18]. Thus, extensively calcified aorta was found in 15.1% (54/358) of the patients enrolled to the inoperable cohort of the PARTNER trial compared to 0.9% (6/699) of the patients enrolled to the TAVR versus SAVR high surgical risk cohort [6, 19]. Rodés-Cabau et al. [7] reported TAVR procedures in 339 patients and defined PA as extensive circumferential calcification of the thoracic aorta as assessed by computed tomography and/or fluoroscopy. PA was present in their cohort in 61 of 339 patients (18%).

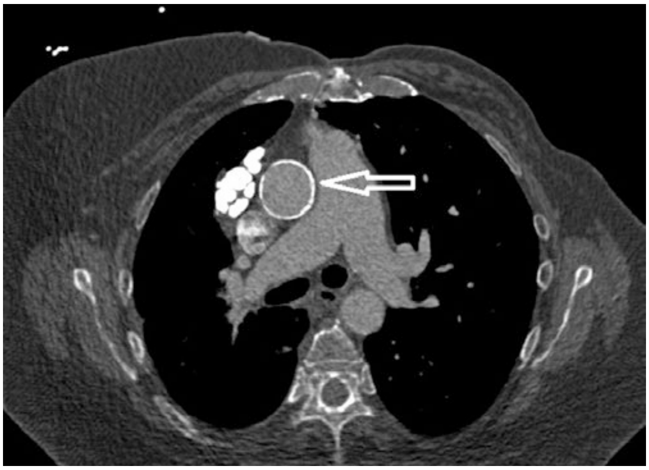

Fig. 63.4 Chest CT demonstrating a near circumferential heavy calcification of the ascending aorta (white arrow) extending to the aortic arch

Amorim et al. [20], suggested the use of the term PA when a circumferential calcification of the thoracic aorta is present at any given level. They proposed classification of PA into Type I if circumferential calcification is present in the ascending aorta independently of further extension and Type II if circumferential calcification is localized only in the aortic arch and/or descending aorta. Type I PA was further subdivided into Type IA when there is no possibility to clamp the aorta during cardiac surgery, and Type IB when clamping is possible but at increased risk. This classification is helpful to guide surgical relevance. The location of the circumferential calcification is crucial in surgical decision-making. While a narrow ring of calcium confined to the mid ascending aorta can be safely managed surgically without extensive modification of technique, complete calcification of the aortic root and/or distal ascending aorta at the base of the innominate artery can mandate a much more extensive operation necessitating aortic root, ascending aorta and partial arch replacement with reimplantation of the coronary arteries under circulatory arrest.

The nonuniformity in the definitions used to describe PA and the absence of this variable from conventional pre-TAVR risk scores (e.g. logistic EuroSCORE or Society of Thoracic

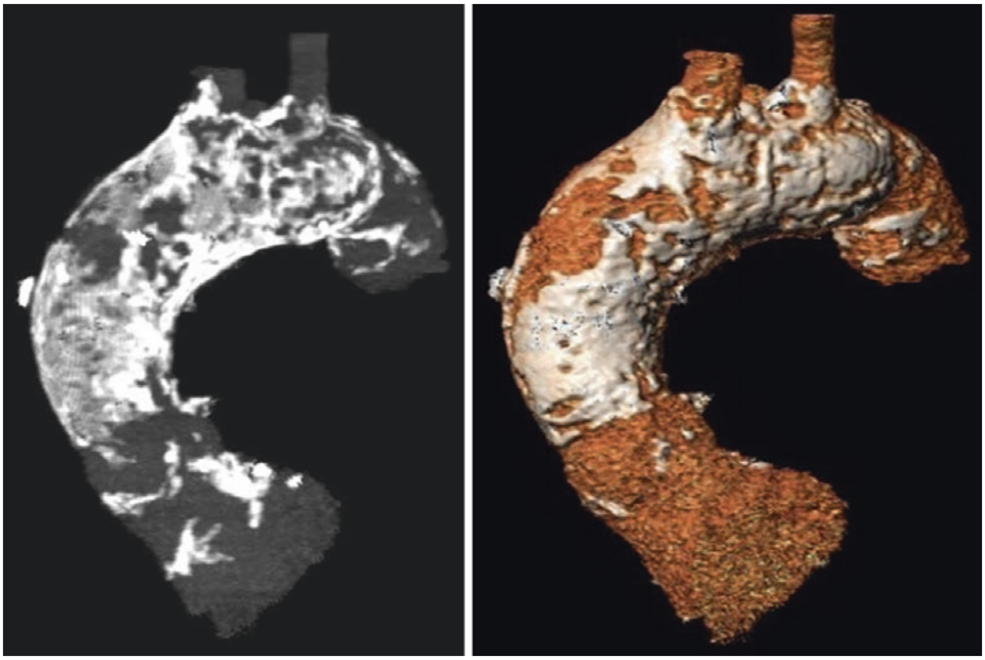

Fig. 63.5 3D reconstruction of aorta showing extensive calcification of the aortic root, ascending aorta and aortic arch

Surgeons score) motivated the Valve Academic Research Consortium (VARC) to emphasize the importance of considering PA in the risk stratification performed by a dedicated heart team [21]. They defined PA or severely atherosclerotic aorta as "heavy circumferential calcification or severe atheromatous plaques of the entire ascending aorta extending to the arch such that aortic cross-clamping is not feasible". Moreover, they also suggest noncontrast axial CT as the imaging tool of choice in order to evaluate calcification of the ascending thoracic aorta and aortic arch.

Pathogenesis and Associations

The pathophysiological mechanisms attributing to the formation of a PA are not fully understood. Two independent processes lead to the formation of aortic calcification:

1. Atherosclerosis that occurs as a result of inflammatory response involving the tunica intima
2. Calcification of mainly the medial layer of the aorta in the absence of atheroma [1].

Calcified PA involving predominantly the aortic media and atherosclerotic intimal plaque with calcifications might be two separate entities with considerable overlap that may also coexist [9].

Atheromatous Aortic Disease: A Disease of the Tunica Intima

As part of the development of atherosclerotic plaques, calcium is deposited in the arterial wall by a process that is histologically similar to bone formation [22]. Mineral deposits predominantly of apatite in the form of hydroxyapatite, carbonate apatite, and calcium-deficient apatite may replace the accumulated remnants of dead cells and extracellular lipid, including entire lipid cores. Atherosclerotic lesions initially contain macrophage foam cells and fatty streaks [22, 23]. They may progress to intermediate and advanced lesions containing scattered collections of extracellular lipid droplets and lipid core respectively. When the lipid core and other parts of the lesion become calcified it may be referred to as type Vb lesion.

Thoracic aortic calcification (TAC) was found to be associated with the conventional cardiovascular risk factors – aging, hypertension, smoking, dyslipidemia and diabetes mellitus [24–26] (Table 63.1). It was also found to be related to coronary artery calcification [25] and increased risk of cardiovascular events and mortality [15, 27].

Table 63.1 Causes of thoracic aortic calcification and porcelain ascending aorta

Cardiovascular risk factors
Aging
HTN
Smoking
Dyslipidemia
DM
Chronic kidney disease
Mediastinal radiation
Systemic inflammatory disease
Takayasu arteritis
SLE
RA

DM diabetes mellitus, *HTN* hypertension, *RA* rheumatoid arthritis, *SLE* systemic lupus erythematosus

Non-atheromatous Aortic Disease: A Disease of the Tunica Media

Ascending thoracic aorta calcification in its extreme form—porcelain aorta, does not necessarily share the exact pathophysiological mechanisms with atherosclerosis [28]. Vascular medial calcification occurs independently of intimal calcification and atherosclerosis [29]. Uremia, radiation or vascular inflammation induces a phenotypic change of vascular smooth muscle cells (VSMC) into osteoblasts [23]. Transformed osteoblasts in the media produce a number of bone associated proteins not normally expressed in the vessel wall. They enable nucleation of mineral crystals by the matrix proteins and concentration of calcium and phosphate in preparation for mineralization [23]. As this process progresses, it can eventually form a dense circumferential sheet of calcium crystal in the center of the media, bounded on both sides by VSMC and often contains bone trabeculae and osteocytes.

The differentiation between intimal atherosclerotic calcification and medial non-atherosclerotic calcification has potentially important clinical implications to the surgical and percutaneous management of valvular and coronary artery disease in patients with PA. The presence of a heavily calcified atheromatous aorta is associated with a significantly increased risk of embolic stroke and peripheral embolism during conventional cardiac surgery [2, 11, 30]. On the other hand, when calcification of the aorta is limited to the tunica media it excludes a significant source of embolization because the intima is relatively intact without exophytic lesions but precludes safe cross-clamping or cannulation of the aorta. Nonetheless, the presently available diagnostic methods used for the detection of TAC including CT do not discriminate intimal from medial calcification thus precluding a clear clinically valuable separation between patients with PA [15, 31].

Summary of the causes of TAC and PA is elaborated in Table 63.1.

Prevalence

PA is usually an incidental finding in patients being evaluated for cardiovascular or pulmonary diseases. The presence of a heavily calcified ascending aorta and/or arch is asymptomatic, a fact that precludes true evaluation of the prevalence of PA in the general population. Inconsistencies in definition and different utilization of diagnostic modalities as mentioned above also restrict the ability to assess the true prevalence of PA. The prevalence of PA was found to be 7.5% in patients evaluated for AS [3], between 1.2% and 13.6% in patients undergoing valvular or coronary revascularization surgeries [4, 10, 32–34] and between 5% and 33% in the patients undergoing TAVR [7].

PA and Cardiovascular Risk

There is growing evidence that identification of ascending aortic and/or aortic arch calcification can also be related independently to higher risk of cardiovascular events and mortality. The largest study that examined the relation between TAC and mortality evaluated a cohort of 8401 asymptomatic individuals that underwent CT scan for the assessment of an underlying coronary heart disease risk [27]. Multivariable analysis revealed that the presence of aortic calcification was independently related to increased mortality during an average follow-up of 5 years (HR = 1.78, $p = 0.002$). When comparing ascending to descending aortic calcification with regards to increased stroke risk there have been contradictory findings. Jacobes et al. [35] found increased risk of stroke only in patients with ascending aortic calcification (AAC) while Tanne et al. [36] found increased risk of stroke only in patients with descending aortic calcification. Furthermore, there is an increased evidence of association between AAC and coronary artery disease [25, 37].

PA and Cardiac Surgery

An important clinical implication of PA is an increased risk of stroke during cardiac surgery due to embolization of atheromatous material caused by manipulation of the ascending aorta [10]. It is well established that atherosclerosis of the ascending aorta diagnosed by palpation or epiaortic ultrasound during cardiac surgery is an independent predictor of short and long-term neurologic events and mortality [33, 38]. Moreover, the presence of heavily calcified PA is associated with a significantly increased risk of cerebral embolism during cardiac surgery [2, 30]. Severe AAC interferes with aortic cannulation, aortic clamping, aortotomy and/or central coronary bypass anastomosis, necessitating modification of the surgical technique to avoid complications such as aortic dissection, surgically unreconstructable ascending aorta or release of thromboembolic material that may cause periprocedural stroke [8, 11, 39].

Several modifications have been used in isolated CABG procedures in order to avoid cannulation and clamping of the diseased ascending aorta. The most common modification is a "no touch" technique totally avoiding manipulation of the ascending aorta. This is most readily accomplished by off pump techniques and all arterial grafting using bilateral internal mammary grafts with the addition of a radial(s) artery as a side "Y" or "T" graft. Alternatively, if the aorta is not totally calcified and a non-calcified area ascertained by epiaortic scanning and palpation, a "clampless" proximal anastomosis can be performed using a "Heartstring" device [4, 34, 40]. Lev-Ran et al. compared retrospectively the results of coronary revascularization between cardiopulmonary bypass (CPB) with femoral artery cannulation in 15 patients and off-pump CABG in 41 patients with PA [40]. There was only one case of perioperative mortality (2.4%) and no case of perioperative stroke or TIA in the off-pump CABG group. The main disadvantage of this strategy in their report was incomplete revascularization in 24.3% of patients. The CPB group had one mortality case (6.6%), three perioperative stroke or TIA (20%) and lower rate of incomplete revascularization (6.6%). Other options include femoral or axillary artery cannulation for CPB [34, 41], intraluminal balloon catheter to substitute external clamps [42], avoiding proximal graft anastomoses on the ascending aorta [43] and CABG performed during deep hypothermic circulatory arrest [44]. Extended procedures such as ascending aorta endarterectomy [45], patch aortoplasty and graft replacement of the ascending aorta [46, 47] have also been described.

Mitral valve procedures can also be performed without aortic cross-clamping by hypothermia and a fibrillating heart [32]. Tricuspid valve and other right-sided procedures can be performed on a beating heart without the need for aortic cross-clamping or manipulation. Aortic valve procedures in patients with severe calcification of the ascending aorta mandate the greatest modification from usual techniques [4]. Techniques for SAVR in patients with PA include SAVR under deep hypothermic circulatory arrest (DHCA) [4, 48]. Using this technique, the ascending aorta can be managed with several strategies: aortotomy low on the ascending aorta if any non-calcified area is present [4]; replacement of the ascending aorta [4, 47] and ascending aortic endarterectomy

[4, 9]. Although most of the procedures can be performed with <20 min of circulatory arrest, there may be some reluctance to perform DHCA in the setting of advanced age and significant comorbidities [49]. Another option used to avoid aortic cross-clamping and manipulation in patients with severe AS is the apico-aortic conduit technique [50, 51]. It is an aortic valve bypass surgery that utilizes a conduit containing a prosthetic valve which relieves AS by shunting blood from the apex of the left ventricle to the descending thoracic aorta. The disadvantages of this technique include the necessity for a sizable left thoracotomy, the fact that it is only feasible if no significant aortic regurgitation is present and a challenge to perform anastomosis of the conduit to the descending aorta in case of concomitant calcified descending aorta which is usually present.

Each of the methods described above for SAVR in patient with severe AS and PA are technically challenging, require significant surgeon experience and do not completely avoid manipulation of the heavily calcified ascending aorta. Therefore, no standard treatment has emerged with surgical management individualized to the particular patient and location and extent of calcification present [1]. There is still a considerable risk of perioperative mortality or stroke among these patients [4]. Interestingly, Nishi et al. [52] evaluated preoperative CT scans of 11 patients with PA and observed that that the calcification grade just below the innominate artery is significantly lower than that at the level of the pulmonary artery, where aortic cross-clamping is usually applied. Calcification in <75% of the circumference was considered sufficient to allow soft cross-clamp of the aorta just below the innominate artery in all 11 patients, and SAVR under CBP with mild hypothermia was completed without periprocedural mortality or stroke.

PA and TAVR

With the evolution of TAVR, a new technology to treat high-risk elderly patients with severe AS that avoids aortic cross-clamping and CPB has become available [18]. Few studies have directly evaluated and reported the impact of PA on outcome of patients after TAVR [2, 5, 7, 18, 53, 54]. Rodés-Cabau et al. [7] were the first to report the impact of PA defined as extensive circumferential calcification of the thoracic aorta as assessed by CT and/or fluoroscopy. From a Canadian registry of 339 patients who underwent balloon-expandable TAVR, 61 patients (18%) had PA. Patients with PA in this study were younger; were more frequently female (75.4% vs. 50.7%) and exhibited a lower STS score. The procedure was successful in 98.4% of the patients with PA but valve malposition requiring implantation of a second valve tended to be more frequent in these patients. The 30-day stroke and mortality rates were similar in patient with and without PA. Patients with PA tended to have a better survival rate at 1-year follow up (86% vs. 74%; p = 0.14).

Pascual et al. [54] reported the results of CoreValve implantation in 449 patients using the transfemoral or trans-axillary approaches. Thirty-six patients (8%) had PA that was diagnosed with fluoroscopy. The procedural success rate was high (97.3%) with no differences in the percentage of malposition or any other periprocedural complication between patients with and without PA. There was no significant difference in 2-year survival between the two groups. In a relatively large German registry, Zahn et al. reported the results of TAVR in 147 (10.7%) patients with PA compared to 1227 patients without PA [53]. The procedural success rate was high in both groups (97.3%), coronary ischemia complicated the procedure more often in patients with PA (2.1% vs. 0.1%), and there was a trend toward a greater 30-day stroke rate (5.5% vs. 2.8; p = 0.08). Thirty-day mortality was higher among patients with PA (12.9% vs. 7.6%; p = 0.03), but multivariate analysis did not show that PA was an independent predictor of in-hospital death or stroke.

Furthermore, a sub-analysis of the inoperable arm of the PARTNER (Placement of Aortic Transcatheter Valves) trial performed by Makkar et al. [18], found PA to be the commonest reason for technical inoperability (39 out of 85 patients; 46%). PA and other reasons for technical inoperability in this study (e.g. mediastinal radiation or chest deformities) were associated with similar procedural outcomes and better 2-year outcome than in patients that were excluded from surgery due to clinical reasons. The comparative data presented above, suggest that unlike in SAVR, PA does not mandate significant procedural modifications and does not affect procedural outcome in TAVR and therefore TAVR is expected to become the standard of care for patients with severe AS and PA. PA is a subset of "technically inoperable" patients who are particularly well suited for TAVR since there are usually no other significant co-morbidities present and the surgical alternatives are usually more extensive than isolated SAVR.

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Cardiovascular Manifestations of Marfan and Loeys-Dietz Syndrome

Florian S. Schoenhoff and Thierry P. Carrel

High Yield Facts

- Fifty percent of patients presenting with acute type A dissection below the age of 40 years have Marfan syndrome (MFS).
- Every year new mutations associated with syndromic and non-syndromic forms of aneurysmal disease are described.
- Prevention of dissection through regular follow-up and prophylactic surgery is key.
- Threshold for elective root surgery in patients without risk factors is 50 mm in MFS and 44–46 mm (CT) in Loeys-Dietz syndrome.
- Risk factors are family history of dissection, rapid growth and severe aortic regurgitation.
- Very little data regarding children and adolescents is available.
- Need for re-interventions in MFS patients is primarily driven by a history of dissection.

Introduction

The last decade has seen an increasing awareness for patients with connective disorders and patients with Marfan syndrome (MFS) in particular. MFS is imposed by mutations in the gene encoding for fibrillin-1 (FBN1). MFS has long been the only seriously considered differential diagnosis in young patients presenting with aortic aneurysms. The advent of multi-gene panel genetic testing and the discovery of new syndromic forms of connective tissue disorders such as Loeys-Dietz syndrome (LDS) as well as many forms of non-syndromic presentations have established thoracic aortic aneurysms as a genetically mediated disease [1–3]. Although the spectrum has broadened, MFS still serves as a model for connective tissue disorders with vascular involvement. Surgical results in patients with MFS provide an important benchmark for other patient populations.

Although thoracic aortic and mitral valve disease are the predominant cardiovascular manifestations in patients with MFS and LDS, patients may also present with cardiomyopathy or aneurysms and dissection of the head and neck vessels (Fig. 64.1).

Proximal Aortic Disease in Marfan and Loeys-Dietz Syndrome

Aneurysms and dissections in MFS and LDS may include any part of the vasculature. The majority of MFS patients develop aortic root aneurysm over time. While there are children that need aortic root replacement, the majority of MFS patients undergo root surgery later in life. In a large series of patients with MFS, the mean age at root replacement was 32.9 years (range, 1.5–73 years) but of course included patients that were unaware of their disease and underwent surgery for acute dissection [4]. While many children and adolescents already have a dilated aortic root with a z-score >3, only few already fulfill the criteria for elective surgery. The current ESC 2014 guidelines recommend elective surgery in Marfan patients without additional risk factors at a diameter of 50 mm [5]. In patients with additional risk such as family history of dissection, diameter increase >3 mm/year or severe aortic regurgitation a cut-off of 45 mm is recommended. The AHA 2010 guidelines also recommend surgery at a diameter of >50 mm but only consider a family history of dissection at smaller diameters or a diameter increase of >5 mm per years as a special risk factor [6]. The AHA guidelines also recommend surgery if the ratio of the cross-sectional area of the aorta divided by the patients' height in meters is >10. In patients with LDS recommendations are still being debated. The 2010 AHA guidelines

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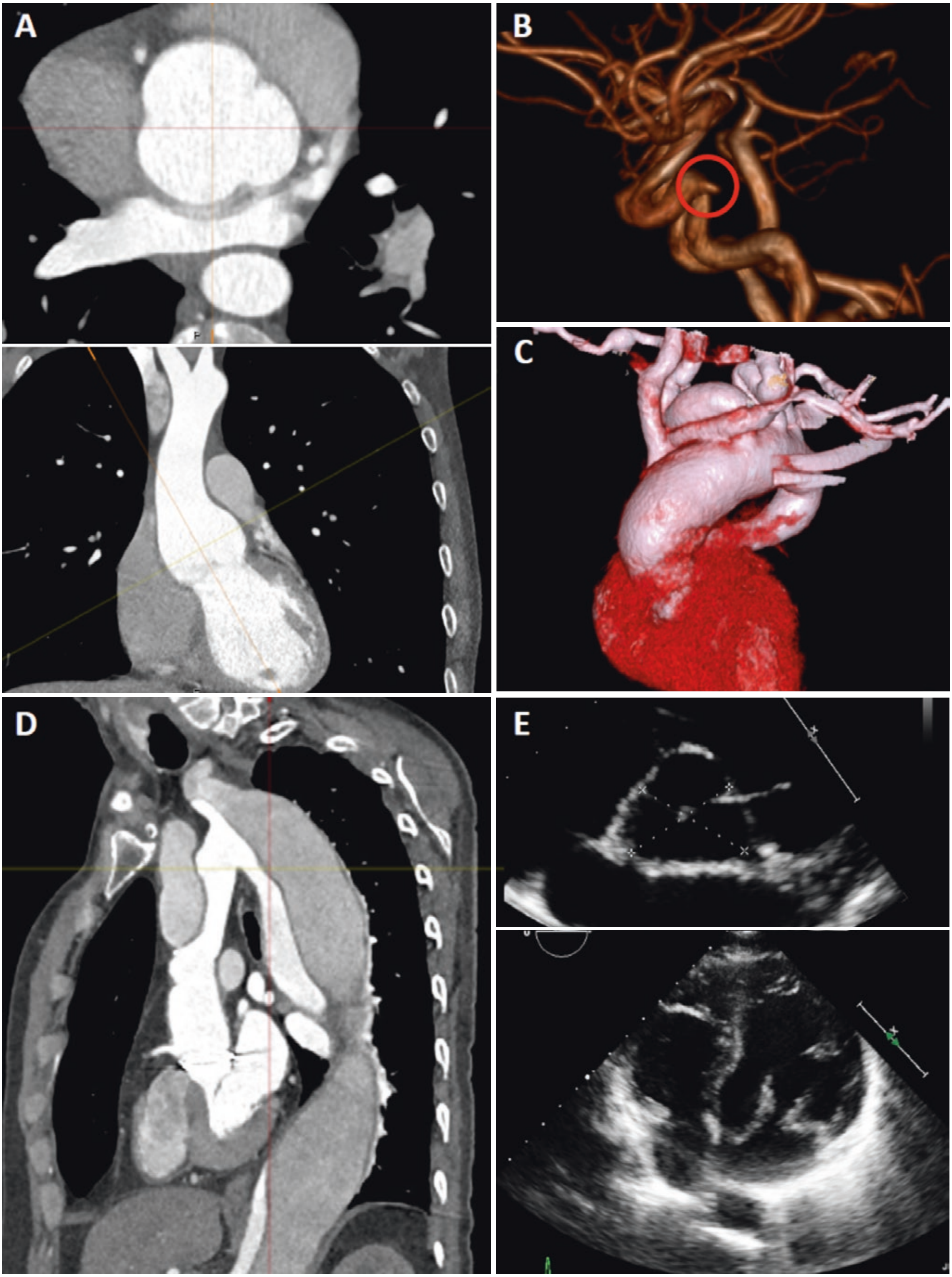
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recommend surgery at a diameter >42 mm as measured by transesophageal echocardiography (TEE) or 44–46 mm by computed tomography (CT). These recommendations pertain to patients shown to have TGFBR1 or TGFBR2 mutations. Meanwhile, several different mutations have been shown to cause the phenotype of LDS and not all of these mutations may carry the same risk for acute dissection as those with TGFβ receptor mutations.

The initial reports of patients with LDS mainly focused on children and adolescents that presented with a very severe phenotype. Unfortunately, the cardiovascular component in these patients was reported to be very aggressive and in the initial reports from the Baltimore group [7, 8], patients frequently dissected well below the accepted surgical threshold of 50 mm for patients with MFS.

In our population of patients diagnosed with MFS based on clinical criteria and mutation analysis of the FBN1 gene before the advent of TGFBR1/2 testing, one-fifth of patients have been retrospectively diagnosed as having LDS. In a series comprising 830 patient-years, LDS patients did not dissect earlier, did not dissect more frequently and did not have a higher need for re-interventions than MFS patients. In our LDS patients, the mean aortic root diameter in patients not presenting with type A dissection was 57 ± 9 mm, with only one patient that underwent surgery as a child [9]. In the initial report from the Baltimore group, the ratio children vs. adults that underwent surgery was 2:1, vascular events frequently occurred at diameters less than 45 mm and in patients younger than age 10, with the youngest being 6 months old [7].

In a large comparative study of 243 MFS and 70 patients with TGFBR2 mutation published by Attias and colleagues, there was no difference between MFS and LDS patients regarding average age at which aortic surgery was performed (35 ± 16 years vs. 39 ± 13 years) as well as incidence of aortic dissection (14% vs. 10%). Mortality was higher in TGFBR2 families before diagnosis, but similar once patients had been diagnosed correctly and underwent surgery [10]. Recently, new mutations in patients sharing phenotypic features with LDS such as SMAD3, TGFB2 and TGFB3 have been identified and it is likely that this will continue [11–13]. The 2014 ESC guidelines recognize the partly conflicting nature of these results and did not give any special recommendation.

There is no clear evidence regarding prophylactic surgery in MFS and LDS patients wishing to become pregnant. The 2010 AHA guidelines recommend surgery in MFS patients with an aortic root diameter >40 mm. The 2014 ESC guidelines recommend surgery at 45 mm. Most patients are in the range between 40 and 45 mm when they present with a wish for pregnancy and counseling can be challenging. There are currently no recommendations other than the ones mentioned above for patients with LDS.

While most surgeons agree that there is a higher likelihood of sparing the valve during aortic root replacement (VSRR), this has not yet translated in a lower threshold for elective surgery in young patients that are eligible for valve-sparing root replacement, such as most MFS and LDS patients.

Elective root replacement using a tube graft with a mechanical valve is a safe operation and has contributed to the increased survival of MFS patients over the past decades [14, 15]. Perioperative complications are rare and operative mortality has become an exceptional event. Furthermore, it is a very durable solution; in our own cohort there was no reoperation on the aortic root. Several studies with large patient populations report a low incidence of thromboembolic complications during follow-up. Cameron and colleagues report that among 372 patients, thromboembolism was the most common late complication after aortic root replacement but only occurred in patients with root replacement using a mechanical valve (MRR). Actuarial freedom from thromboembolism was 96.3%, 93.3%, 91.0% and 89.8% at 5, 10, 15, and 20 years, respectively [4].

Although most studies suffer from uneven follow-up, VSRR has already demonstrated superiority in terms of thromboembolic events and bleeding. The Hopkins group compared outcomes in 140 MFS patients undergoing either MRR (n = 56) or VSRR (n = 84). Thromboembolic events were significantly more frequent in the MRR group (9% vs. 1%, $p = 0.03$) but the rate of dissection, which certainly influences the thromboembolic rate, was much higher in the MRR group (16% vs. 1%, $p = 0.001$) [15]. Although some surgeons expressed their views that MFS itself is not a risk factor for VSRR failure anymore [16], a large international registry from the Aortic Valve Operative Outcomes in Marfan Patients Study Group found that outcome of VSRR in MFS is mostly likely different than in non-MFS patients [17]. After including 316 MFS patients from experienced centers, 7% of VSRR patients had developed grade 2 AR after the first year, which is a worse outcome compared to non-MFS patient populations. In our own patient population, the annual failure rate of VSRR is actually lower than the risk for thromboembolic event or stroke [18]. Obviously, such analysis are severely

Fig. 64.1 (**a**) Forty years old Loeys-Dietz syndrome (LDS) patient with SMAD3 mutation and emergency repair of iliac artery aneurysms and unrepaired aortic root aneurysm. (**b**) Aneurysm of the internal carotid artery at the origin of the anterior chorial artery in a 9 years old LDS patient with a TGFBR2 mutation. (**c**) Arterial tortuosity in a 4 years old patient with suspected LDS presenting with aortic root and arch aneurysm. (**d**) 53 years old Marfan syndrome (MFS) patient presenting with complex thoraco-abdominal aneurysm 14 years after aortic root replacement for type A aortic dissection. (**e**) 19 years old MFS patient with moderate mitral valve insufficiency and only mildly dilated aortic root limited by the low occurrence rate of both events, but similar to results from a large meta-analysis which analyzed 11 observational studies reporting valve-related morbidity and mortality after MRR or VSRR in patients with MFS and a study size n > 30 to reflect the centers experience [19]. Outcomes after VSRR depend on patient characteristics, surgical skills and aggressiveness with which the approach is pursued. Therefore, to be able to make an informed decision, the surgeon and the patient have to consider the expected failure rate after VSRR and compare it to the rate of thromboembolic events after MRR, which may also vary according to patients characteristics in each center.

Acute Aortic Dissection in Marfan Patients

Acute aortic dissection (AAD) due to aortic aneurysms is still the leading cause of death in this patient population. Although major advances in surgical and intensive care management have been achieved in the last decades, emergency aortic root surgery is associated with a significant worse outcome compared to an elective approach. In a multi-institutional series of 675 MFS patients 30-day mortality for elective repair, urgent repair or emergency repair was 1.5%, 2.6%, and 11.7% respectively [20]. Low morbidity and mortality rates in MFS patients undergoing elective root surgery have fostered the concept of prophylactic aortic surgery to prevent AAD and its sequelae [21]. As a consequence of this strategy, life expectancy in MFS patients has dramatically improved over the past decades through prevention of acute dissection [4].

Nevertheless, despite the wide availability of screening and prophylactic surgery, 36% of MFS patients operated on in our institution initially presented with acute dissection.

The incidence of MFS patients initially presenting with type A dissection in published series varies widely from 4.4% to 28% depending on the patient population [4, 22]. In large US centers such as Johns Hopkins Hospital, a large proportion of patients is referred for elective surgery from all over the country and therefore, the number of patients presenting with AAD is relatively low compared to some of the European centers were patients with type A dissection are directly referred to large tertiary care centers.

The optimal strategy for repair of type A dissection in MFS patients has to take into account future developments of the non-repaired aortic segments. If the patient is known to have MFS or if there is a high likelihood for any kind of connective tissue disorder, the risk for re-operation is very high if the root is not replaced. In the IRAD registry, the prevalence of MFS in patients presenting with AAD below the age of 40 was almost 50%. While surgery for type A dissection is primarily life-saving surgery, replacement of the entire root is strongly recommended and any form of Yacoub-type repair is discouraged. Whether valve-sparing root surgery should be performed depends on the individual setting, patient related factors, center and surgeons' experience.

As in non-MFS patients, the fate of the aortic arch in MFS patients presenting with type A aortic dissection is strongly correlated with the extent of the initial surgery. It has been clearly shown that not replacing the entire ascending aorta using hypothermic circulatory arrest results in a high rate of re-interventions. Therefore, performing a tear-oriented hemiarch replacement at the minimum is strongly recommended. Nevertheless, the additional burden of replacing the entire aortic arch as an adjunct to emergent proximal repair is not very well defined and makes comparison with patients undergoing elective total arch replacement at a later time point difficult.

The major risk factor for the need of re-intervention on the aortic arch and distal aorta after repaired type A dissection is a patent false lumen. Therefore, several groups began to advocate total arch replacement and implantation of a frozen elephant trunk (FET) in addition to proximal repair in type A dissection. In a series of 44 MFS patients that underwent total arch replacement with implantation of a FET mortality was 4.8% over a mean follow-up of 3 years and only one neurologic event. Nevertheless, the rate of patients with chronic type A dissection was very high with 57% and most likely does not reflect general practice [23]. Although primary technical success using a FET is certainly feasible, there are concerns that continued dilation of the aorta around the stent graft will limit the durability of the repair [24].

A French group [25] reported that in their MFS series secondary total arch replacement had to be performed in 16% after elective root surgery and in 73% of patients after type A dissection compared to 3% and 33% in our own patient population [26]. We have shown that the extent of arch surgery during the initial intervention did not influence the need for thoraco-abdominal repair during follow-up. This suggests that it is the dissection itself that drives the need for re-operations in these patients and that the aortic arch is only one of many segments that have to be repaired over the years. Replacing the aortic arch during initial surgery for AAD obviously spares the patients from secondary total arch replacement but it does not protect MFS patients from re-operations on primarily non-treated aortic segments ultimately leading up to replacement of the entire aorta. Furthermore, up to two-thirds of MFS patients after AAD will never need additional arch procedures if the proximal arch was addressed during the initial surgery.

Considering the advances in aortic surgery over the past decade, even complex re-operations seem to carry a moderate risk if performed in an elective setting. Therefore, delaying major additional procedures during initial surgery for acute dissection until they can be performed more safely under elective circumstances is certainly an option.

Interventions on the Distal Aorta After Type A Dissection

Patients with MFS frequently must undergo interventions on the distal aorta [14, 27, 28]. In our own experience, nearly half of the patients with acute aortic dissections had to undergo interventions on the distal aorta during a mean follow-up of 9 years. Re-interventions on the distal aorta after proximal repair due to type A dissection are mostly precipitated by residual dissection in the downstream aorta. Type B dissection poses a serious threat for MFS patients undergoing elective root repair throughout follow-up. The vast majority of patients undergoing interventions on the distal aorta after elective proximal aortic repair suffered from type B dissection in the meantime. In a cohort of MFS patients with a history of aortic dissection, 52% of patients experienced a clinical event, defined as new aortic dissection, surgery, ischemia, hemorrhage, within a follow-up period of 9.8 years [29].

Aortic Dissection in Patients with Loeys-Dietz Syndrome

In 2005, LDS emerged as a connective tissue disorder with an aggressive vascular phenotype caused by TGFβ receptor defects [7]. In the initial reports from the Baltimore group, the mean age at death was 26 years and 1/3 of patients presenting with dissection or death were younger than 19 years and as young as 6 months of age. Patients frequently dissected with aortic root diameters of less than 40 mm, which made it difficult to give recommendations regarding thresholds for surgery. Meanwhile, several mutations in genes encoding for proteins interacting with the TGFβ pathway have been associated with LDS. The available data suggests that the risk for dissection might be different depending on the mutation with patients carrying a TGFBR2 mutation being at a higher risk for dissection than those with a SMAD3 mutation. While it has been shown that LDS patients initially being treated as having MFS did not have a worse outcome, it seems especially important to leave as little residual aortic tissue during the initial surgery as possible, i.e. always to replace the root and to use separate grafts if the arch has to be replaced. In a large series from Baltimore, a high percentage of patients needed to undergo re-intervention if the proximal arch was not addressed during the initial surgery [30].

Mitral Valve Disease in Marfan and Loeys-Dietz Patients

MFS patients frequently exhibit anomalies of the mitral valve including thickening of the leaflets, excessive leaflet tissue but also structural deformities of the valvular and subvalvular apparatus such as annular dilation and elongation of the chordae tendinae [31–33]. It has been speculated that continued shear stress of the leaflets leads to endothelial activation and subsequent tissue overgrowth as a pathological form of compensation [34]. More recent research has demonstrated the influence of excessive TGFβ signaling not only on aortic aneurysm formation but also on mitral valve pathology, as abrogation of TGFβ signaling by using TGFβ neutralizing antibodies ameliorates the mitral valve phenotype in a mouse model of MFS [35]. Data obtained using cultured human cells from patients undergoing mitral valve surgery also suggests a role of TGFβ in patients presenting with mitral valve prolapse (MVP) not necessarily associated with MFS [36].

While certainly being a continuum, the cardiovascular phenotype in children with a severe form of MFS is different from adult patients. Children frequently present with severe mitral valve insufficiency with annular dilation and some form of cardiomyopathy that has not been defined yet, whereas in adults, aortic root dilation is the leading cause for surgery. In children with MFS, the mitral valve is the major cause of morbidity and mortality [37–39].

There is again very little data regarding mitral valve disease in patients with LDS. In a recently published report from Norway, the authors found a difference in the occurrence of MVD depending on the underlying mutation. While MVD in the overall population was rare, it was frequently seen in patients with a mutation in SMAD3 [40]. Patients with SMAD3 mutation are thought to have a less aggressive vascular phenotype than those with TGFβ receptor mutations.

Although MVP with mild insufficiency is very common in MFS, in our experience only 15% of these patients needed surgery on the mitral valve during follow-up. The etiology of mitral regurgitation in MFS is prolapse of the anterior leaflet (~90%), the posterior leaflet (~30%) or both (~50%), accompanied by annular dilatation [41]. Recent reports from patients with Barlow disease undergoing mitral valve surgery suggest that successful repair can be achieved in the vast majority of patients even in the presence of complex lesions [42]. Jouan and colleagues report a 95% repair rate in patients undergoing primary surgery for Barlow disease with an overall survival of 89% and a freedom from re-intervention of 95% at 8 years [43]. Although there are differences in patients with mitral valve prolapse when comparing MFS and non-MFS patients [43], Rybczynski and colleagues have shown that factors predicting progression of mitral valve regurgitation as well as adverse outcomes are the same for both populations. In their study they followed 112 MFS patients with moderate or less mitral valve regurgitation at base line and identified flail-leaflet and increased end-systolic LV diameters as independent risk factor for progression of mitral valve regurgitation in multivariate analysis [44].

In our experience over the past 15 years, isolated mitral valve surgery was performed in 57% and in combination with root surgery in 43%. Mitral valve reconstruction was performed in 36% and mitral valve replacement in 64%.

In a review on children undergoing mitral valve surgery, Cameron and colleagues presented original data on nine children operated on between 1978 and 1995. Mitral valve repair was performed in six and replacement in three patients. Repair techniques used where the same as in the adult population. Two patients in the group with mitral valve repair had to undergo reoperation due to severe left ventricular dilation, stressing the malignant nature of severe mitral valve disease in children with MFS [45].

Cardiomyopathy in Marfan and Loeys-Dietz Patients

As already discussed above, mitral valve disease and poor LV function are the main reasons for mortality in children with Marfan syndrome. Over the past decade, several reports highlight that many patients with MFS exhibit some form of LV impairment that is not attributable to valvular heart disease alone. In a series of 234 patients without significant valvular regurgitation or previous root repair, only 7% of patients had a dilated LV and none of these fulfilled the criteria for dilated cardiomyopathy [46]. Nevertheless, Hetzer and colleagues reported a higher than expected rate of MFS patients in their population of patients undergoing heart transplant [47].

Aneurysms of the Head and Neck Vessels in Loeys-Dietz Patients

Arterial tortuousity was one of the key features when LDS was initially described. Patients frequently present with marked tortuousity of the supra-aortic branches and frequently need surgery for dilatation during arch repair. In an early report from Baltimore including 25 patients, 8 patients had intracranial aneurysm and 3 had dissection of the carotid and vertrebrobasilar arteries [48]. It should be noted that many LDS patients also demonstrated other neuroanatomic abnormalities such as hydrocephalus, Chiari malformation or craniosynostosis. In a more recent retrospective study looking at patients with connective tissue disorders undergoing cranial imaging over a 10 year period, 14% of MFS and 28% of LDS patients had some form of intracranial saccular or fusiform aneurysms [49]. While this is in line with other reports, the significance of these aneurysm and the risk of rupture or dissection remains unclear. So far, there are only scattered reports on interventions on these aneurysms.

Conclusion

Cardiovascular abnormalities are the major cause of morbidity and mortality in MFS and LDS. The major cardiovascular manifestation in these connective tissue disorders is a progressive dilatation of the ascending aorta, leading to aortic aneurysm formation and eventually to fatal aortic rupture or dissection. Aortic dissection in early adult life is the leading cause of death in MFS and LDS. Early diagnosis of individuals at risk of the disease is extremely important as timely treatment of cardiovascular complications has greatly improved life expectancy for patients with MFS and LDS.

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Part V

Mechanical Circulatory Support and Transplantation

65

Pharmacologic Support of the Failing Heart

Haifa Lyster and Georgios Karagiannis

High Yield Facts

- Heart failure (HF) is classified based on the left ventricular ejection fraction (LVEF) into HF with reduced LVEF (HFrEF) and HF with preserved LVEF (HFpEF).
- In HFrEF the treatment mainly focusses on the inhibition of the sympathetic nervous system and renin-angiotensin-aldosterone system.
- The backbone of treatment of HFrEF is neurohormonal consisting of an angiotensin converting enzyme inhibitor, a beta blocker and a mineralocorticoid receptor antagonist.
- Randomised controlled clinical trials have shown the neurohormonal approach to be effective in improving both mortality and quality of life.
- Relatively newer drugs, such as ivabradine and sacubitril/valsartan are also important in the conservative treatment algorithm of HFrEF.
- The therapeutic approach of HFpEF includes adequate blood pressure control, the treatment of possible underlying myocardial ischemia and the adequate control of the ventricular response in atrial fibrillation.
- Inotropes can improve HF haemodynamics in the short-term but are associated in the mid-to long-term with arrhythmias, myocardial ischemia and increased mortality.
- The pharmacological treatment of acute HF mainly consists of intravenous diuretics, intravenous nitrates and, if there are signs of hypoperfusion, short-term inotropes.

Introduction

Heart failure (HF) is defined as the inability of the heart due to structural or functional abnormalities to achieve adequate blood supply to meet the metabolic needs of the organs or the achievement of adequate blood supply only by increasing the diastolic pressure [1]. HF is a complex clinical syndrome characterized by symptoms at rest or on exertion and clinical signs of cardiac dysfunction [2]. The diagnosis of the syndrome is not always straightforward, as many of the symptoms and signs can accompany other clinical disorders, but it is based on the detection of elevated natriuretic peptides and an abnormal echocardiogram in patients with suspicious symptoms for HF [3].

The classification of HF is based on the calculated left ventricular ejection fraction (LVEF) on the echocardiogram. The old terms of “systolic” and “diastolic” HF have recently been replaced by the terms “heart failure with reduced ejection fraction” (HFrEF) and “heart failure with preserved ejection fraction” (HFpEF) [4]. The cut-off point for the LVEF is 40% with patients having a LVEF <40% considered to have HFrEF.

The most common cause of HFrEF is underlying coronary artery disease, which is responsible for up to two thirds of the cases, followed by hypertension and diabetes mellitus [5]. Other causes include myocarditis, alcohol misuse, chemotherapy or idiopathic dilated cardiomyopathy. Patient with HFpEF on the other hand have different epidemiological and pathophysiological characteristics. They are usually older, more often female, have increased BMI and suffer less often from coronary artery disease and more often from hypertension and atrial fibrillation than patients with HFrEF [6, 7].

The pathophysiology of the cardiac dysfunction in HFrEF is mainly related to the reduction of the left ventricular contractility as a result of a myocardial insult (myocardial infarction, direct

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injury due to a viral infection or toxins, prolonged pressure or volume overload) and the activation of compensatory mechanisms, which initially support but subsequently worsen the myocardial function. These mechanisms include the activation of the sympathetic nervous system (SNS) and of the renin-angiotensin-aldosterone system (RAAS). During the initial phase of HF, the above result in changes in the cardiac dimensions, shape, wall thickness and gene expression, a process which is known as remodeling. The remodeling process initially helps the heart maintain its function without any associated increase in the intra-cardiac pressures. However, the prolonged activation of the SNS and the RAAS and the altered cardiac structure will eventually cause increased cell apoptosis, ischemic cell necrosis, which worsens the left ventricular function even further creating the vicious cycle of progressive cardiac dysfunction and HF symptom development. In patients with HFPEF the most important pathophysiological mechanism seems to be the increased myocardial stiffness as a result myocardial inflammation secondary to comorbid disorders, such as hypertension and diabetes [8].

The pharmacological treatment of HF mainly consists of medications that suppress the maladaptive mechanisms described above. In HFrEF the treatment mainly focusses on the inhibition of the SNS and RAAS, whereas in HFpEF the main goal is to control the comorbidities.

Heart Failure with Reduced Ejection Fraction (HFrEF)

Drugs Which Prolong Survival

The backbone of treatment of HFrEF is neurohormonal consisting of an angiotensin converting enzyme inhibitor (ACEI), beta blocker and a mineralocorticoid receptor antagonist (MRA). Randomised controlled clinical trials (Table 65.1) have shown this approach to be effective in improving both mortality and quality of life and have led to the current guidelines (NICE, ESC, AHA) [9–11]. The currently proposed initial approach to a patient with HFrEF includes the initiation of and ACEI and a beta blocker, which are then gradually up-titrated to the maximum tolerated evidence-based doses. If the patient remains symptomatic and the LVEF is ≤35% an MRA is added to the treatment regimen, which also requires gradual up-titration. If the symptoms are persistent the therapeutic options are either the replacement of the ACEI with an Angiotensin Receptor-Neprilysin Inhibitor (ARNI) or the addition of Ivabradine (provided that the patient is in sinus rhythm at a rate of ≥70 bpm [1].

RAAS Inhibitors (ACE-I, ARB, ARNI): ACEIs prevent the conversion of angiotensin I–II and inhibit bradykinin degradation, there is extensive evidence supporting the use of ACEIs in the treatment of HFrEF including the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) and the Studies of Left Ventricular Dysfunction (SOLVD). The ACEI is to be started at a low dose and then titrated upwards at short intervals e.g. every 2 weeks until the target or maximum tolerated dose is achieved (NICE). Adverse effects such as hypotension, renal impairment, hyperkalaemia can often be avoided by the cautious initiation and subsequent regular monitoring of the blood pressure, urea, creatinine and electrolytes. A dry cough occurs in approximately 10% of patients and is the most common cause cited for switching to an Angiotensin Receptor Blocker (ARB). ACEIs with proven effectiveness in HFrEF are: Captopril (Starting Dose, SD—6.25 mg tds; Target Dose, TD—50 tds), Enalapril (SD 2.5 mg bd; TD 20 mg bd), Lisinopril (SD 2.5–5 mg od; TD 20–35 mg od), Ramipril (SD 2.5 mg od; TD 10 mg od), Trandolapril (SD 0.5 mg od; TD 4 mg od) [1]. ARBs with proven effectiveness in HFrEF are: Candesartan (SD 4–8 mg od; TD 32 mg od), Valsartan (SD 40 mg bd; TD 160 mg bd), Losartan (SD 50 mg od; TD 150 mg od) [1]. The only available ARNI is Sacubitril/Valsartan (SD 49/51 mg bd; TD 97/103 mg bd) [1].

ARBs do not inhibit bradykinin degradation and hence are recommended to reduce morbidity and mortality as an alternative in those patients intolerant to ACEIs because of angioedema or cough. The combination of an ACEI and ARB is no longer recommended following evidence of harm due to adverse effects such as hypotension, hyperkalaemia and renal dysfunction [12–14].

An Angiotensin Receptor-Neprilysin Inhibitor (ARNI) is a new drug class available for the treatment of HF, the first of which is Sacubitril/Valsartan which is a combination of the ARB, valsartan, and a neprilysin inhibitor, sacubitril. Inhibiting neprilysin results in increased levels of several vasoactive peptides such as natriuretic peptides and bradykinin thereby contributing to the neurohormonal approach in managing HF. Clinical trials combining enalapril, an ACEI, and neprilysin caused serious angioedema [15, 16]. Hence, Sacubitril/Valsartan was designed to minimize the risk of angioedema, in the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial Sacubitril/Valsartan was superior to enalapril in reducing mortality and hospitalization for HF [17]. Because of this trial and with regards to safety, an ARNI is recommended in patients who are symptomatic despite taking an ACEI or ARB to further reduce morbidity and mortality. The ARNI should be commenced at least 36 h after the last dose of the ACEI to avoid angioedema.

Beta blockers: Beta blockers modify the neurohormonal changes in HF, sympathetic activation occurs in HF and while this increases heart rate and myocardial contractility over time this leads to deleterious effects on the heart function. Numerous clinical trials have demonstrated the benefits of beta-blockers such as the Cardiac Insufficiency Bisoprolol Study II (CIBIS II) [18] and Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF) [19]. As with ACEIs these are to be commenced at a low dose and then titrated upwards assessing heart rate and blood pressure before and after each dose increment. Beta blockers with proven effectiveness in HFrEF are: Bisoprolol (SD 1.25 mg

Table 65.1 Key trials where drug therapy has been shown to improve prognosis in systolic heart failure or asymptomatic LV impairment

					Reported background drug therapy (%)					
Trial (year)	Study population	Drug	Starting dose	Target dose	Diuretic	Digitalis	Vasodilator	ACEI	AT II RB	β-blocker
ACEI										
Consensus (1987) [27]	NYHA IV	Enalapril	1.25 mg bid	20 mg bid	98	93	~46			3
SOLVD (1991) [28]	CHF, LVEF < 35%	Enalapril	2.5 mg bid	10 mg bid	85	67	51			7
V-HeFT-II (1991) [24]	Peak VO_2 < 25 ml/kg/min LV impaired (EF < 45%)	Enalapril[a]	5 mg bid	10 mg bid	N/R[a]	N/R[a]	[a]			N/R
SAVE (1992) [29]	Post-MI, NYHA I, II LVEF < 40%	Captopril	6.25–12.5 mg tds	50 mg tds	35	26	~51			35
AIRE (1993) [30]	HF post MI	Ramipril	2.5 mg bid	5 mg bid	60	12	56			22
TRACE (1995) [31]	Post MI LVEF < 35%[b]	Trandolapril	1 mg od	4 mg od	66	27	~53			16
β-blockers										
US Carvedilol Study (1996) [32]	NYHA II–IV LVEF < 35%	Carvedilol	3.125 mg bid	25–50 mg bid	95	90	32	95	N/R	
Australia/New Zealand (1997) [33]	IHD NYHA II–III LVEF < 45%	Carvedilol	3.125 mg bid	25 mg bid	~75	38	N/R	~85	N/R	
CIBIS-II (1999) [18]	NYHA III–IV LVEF ≤ 35%	Bisoprolol	1.25 mg od	10 mg od	~98	~52	58	96	N/R	
MERIT-HF (2001) [19, 34, 35]	NYHA II–IV LVEF < 40%	Metoprolol CR/XL	12.5 mg od	200 mg od	~90	~63	N/R	~89	~6	
COPERNICUS (2001) [36]	NYHA III–IV LVEF < 25%	Carvedilol	3.125 mg bid	25 mg bid	99	66	N/R	(97)[c]	(97)[c]	
CAPRICORN (2001) [37]	Post MI LVEF ≤ 40%	Carvedilol	6.125 mg bid	25 mg bid	N/R	N/R	N/R	~97	N/R	
Aldosterone receptor antagonists										
RALES (1999) [38]	NYHA III–IV LVEF ≤ 35%	Spironolactone	25 mg od	25–50 mg od	100	~73	N/R	~94	N/R	~10
EPHESUS (2003) [21]	Post MI HF or diabetes LVEF ≤ 40%	Eplerenone	25 mg od	50 mg od	~60	N/R	N/R	(~86)	(~86)	75
EMPASIS-HF (2011) [22]	NYHA II LVEF ≤ 35%	Eplerenone	12.5 or 25 mg od	25 mg or 50 mg od	84.3	26.6	N/R	78.3	19.1	86.6
Angiotensin II receptor blockers										
CHARM-Alternative (2003) [39]	NYHA II–IV LVEF ≤ 40% ACEI intolerant	Candesartan	4–8 mg od	32 mg od	85	~45	~42	0		54
CHARM-Added (2003) [13]	NYHA II–IV LVEF ≤ 40% On an ACEI	Candesartan	4–8 mg od	32 mg od	90	~58	~37	100		~55
Valiant (2003) [40][d]	Post MI LVEF ≤ 35%[e]	Valsartan	20 mg bid	80 mg bid	~50	N/R	N/R	~39		70

(continued)

Table 65.1 (continued)

Trial (year)	Study population	Drug	Starting dose	Target dose	Reported background drug therapy (%)					
					Diuretic	Digitalis	Vasodilator	ACEI	AT II RB	β-blocker
Vasodilators										
African-American Heart Failure Trail (2004) [25]	African descent NYHA III–IV LVEF ≤ 35% or <45% with dilated ventricle	Fixed ratio isosorbide-dinitrate + hydralazine	(20 mg + 37.5 mg) tds	(40 mg + 75 mg) tds	90	59		69	17	74
Ivabradine										
SHIFT (2010) [26]	NYHA II–IV LVEF ≤ 35% Resting HR ≥ 70 bpm	Ivabradine	5 mg bd	7.5 mg bd	84	22	N/R	79	14	89
Angiotensin-neprilysin inhibitor										
PARADIGM-HF (2014) [17]	NYHA II–IV LVEF ≤ 40% Beta-blocker + ACE-I or ARB	Sacubitril/Valsartan	100 mg bd	200 mg bd	80.3	29.2	N/R	78^f	22.2^f	93.1

N/R not reported

[a] Control drug was ISDN + hydralazine; treatment with a diuretic and digoxin was optimised before randomisation

[b] Wall motion index <1.2

[c] On either and ACEI or ARB

[d] Factorial design that demonstrated non-inferiority to captopril

[e] LVEF ≤ 35% on echocardiogram or contrast ventriculography; ≤40% on radionuclide ventriculography

[f] Pretrial use of ACE-I or ARB

od; TD 10 mg od), Carvedilol (SD 3.125 mg bd; TD 25 mg bd), Metoprolol succinate CR/XL (SD 12.5-25 mg od; TD 200 mg od), Nebivolol (SD 1.25 mg od, TD 10 mg od) [1].

Mineralocorticoid receptor antagonists: Activation of mineralocorticoid receptors by aldosterone and glucocorticoids can worsen heart failure. In the Randomized Aldactone Evaluation Study (RALES) spironolactone reduced mortality and frequency of hospital readmissions when added to standard therapy of an ACEI, diuretics with or without digoxin compared with placebo [20]. Together with the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) [21], where eplerenone reduced improved mortality and hospitalisation for HF, MRA treatment has become established in HF (NYHA class III and IV) guidelines. In the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial, eplerenone significantly reduced cardiovascular mortality and hospitalization for HF as compared with placebo in patients with HFrEF and milder symptoms (NYHA Class II) [22] leading to its recommendation in HFrEF (NYHA class II–IV) unless there are any contraindications. Renal function and serum potassium should be closely monitored in patients on combined ACEI (or ARB) and an MRA. MRAs with proven effectiveness in HFrEF are: Spironolactone (SD 25 mg od; TD 50 mg od), Eplerenone (SD 25 mg od; TD 50 mg od) [1].

Hydralazine and nitrates: Early trials were unable to show a benefit for the use of hydralazine and isosorbide dinitrate (H-ISDN) in HFrEF [23, 24], however, in the African-American Heart failure Trial (A-HeFT), H-ISDN demonstrated a significantly reduced mortality compared with placebo in black HFrEF patients on optimal therapy (ACEI/ARB, beta-blocker and MRA) leading to the study being terminated early [25]. The combination of H-ISDN is recommended in HFrEF who are unable to tolerate a RAAS inhibitor (ACEI, ARB or ARNI) secondary to hyperkalemia or renal dysfunction and as in addition to standard HF therapy in black patients with HFrEF (NYHA Class II or IV).

Ivabradine: Raised resting heart rate is known to be a risk factor for adverse cardiovascular outcomes in patients with HF, Ivabradine is specific inhibitor of the If current in the sinoatrial node slowing down sinus rhythm. In the Systolic Heart Failure Treatment with If Inhibitor Ivabradine Trial (SHIFT) patients with HFrEF with a heart rate of ≥70 bpm on stable HF medication, including a beta blocker if tolerated were randomly assigned to ivabradine or placebo [26]. The use of ivabradine resulted in a significant reduction in mortality and hospitalization due to HF compared to placebo. Due to the results of the SHIFT study, ivabradine is recommended in symptomatic patients with HFrEF, in sinus rhythm with a heart rate of ≥70 bpm despite optimised HF treatment with ACEI (or ARB or ARNI), MRA and a beta blocker if tolerated. The starting dose of Ivabradine is 5 mg bd and can be up-titrated to 75 mg bd [1].

Drugs Which Do Not Prolong Survival but Improve the Symptoms

Certain medications are used regularly in HF because they improve the patients' symptoms and reduce the number of hospitalizations for HF.

Diuretics: The diuretic treatment is essential in the management of congestive HF, as it promotes diuresis, it limits the water retention, it reduces the peripheral edema and the central venous pressure [41]. Most of the diuretic drugs used in clinical practice in the setting of HF act on the loop of Henle (Furosemide, Bumetanide, Torasemide), whereas others act on the distal tubule (thiazides, metolazone) or the collecting ducts (amiloride). Loop diuretics have the most potent diuretic effect and work by blocking the reabsorption of sodium and potassium. The diuretics acting on the distal tubule have a more prolonged effect duration but are less effective as diuretics. Their effect practically disappears when the glomerular filtration rate is <30 ml/min. Finally, drugs such as Amiloride increase the reabsorption of potassium. Common side effects of the diuretics are hypokalemia, hypomagnesemia, hyperkalemia, RAAS activation, dehydration, prerenal azotemia [42].

Digoxin: Digoxin inhibits the sodium potassium adenosine triphosphatase, which controls the Na+/K+ pump mainly in the heart but also in other organs. It exerts a mechanical effect as it enhances myocardial contractility. It has been found to improve the symptoms and reduce the morbidity of HF without reducing the mortality, provided that the plasma levels of the drug are therapeutic (<1.0 ng/mL) [43]. Patients with HF and atrial fibrillation may also benefit from digoxin use to control the ventricular response once the up-titration of the beta-blocker is no longer feasible.

Heart Failure with Preserved Ejection Fraction (HFpEF)

No therapeutic intervention to-date has reduced the morbidity and mortality in HFpEF in randomised controlled trials. Most of the guidelines are based on expert opinion [44]. The effective therapeutic approach of a patient with HFpEF should include:

(a) adequate blood pressure control.
(b) treatment of possible underlying myocardial ischemia.
(c) adequate control of the ventricular response in atrial fibrillation.

Several of the medications used in HFrEF are used in HFpEF as well for different reasons. More specifically:

- The beta blockers improve the ventricular filling by reducing the heart rate and thus increasing the time of diastolic relaxation. They are used effectively in HFpEF patients with atrial fibrillation to control the heart rate and the blood pressure. A small percentage of the patients included in the SENIORS clinical trial, which showed moderate reduction of the composite endpoint of total mortality or hospitalization, had an LVEF of ≥50% [45].

- Diuretics are used to manage the sodium and water retention and to relieve from the breathlessness and peripheral oedema. Usually, smaller doses of diuretics are required in HFpEF compared to HFrEF.
- ACEI and ARBs can theoretically reverse the left ventricular hypertrophy after prolonged use, improving the ventricular filling and relaxation. However, all randomised trials with ACEI/ARBs in HFpEF did not reveal any mortality benefit, as was the case with the MRAs [46–50].
- Digoxin is contraindicated in HFpEF when patients are in sinus rhythm [51]. However, it can be used for heart rate control in patients with fast atrial fibrillation.
- Calcium blockers with negative inotropic effects (diltiazem, verapamil) can also be used to control the ventricular response in patients with HFpEF and atrial fibrillation [52, 53].

Advanced Heart Failure

Clinically available inotropes increase myocardial contractility by several mechanisms, the majority by increasing the intracellular level of cyclic adenosine monophosphate (cAMP) by either stimulating β1 receptors e.g. dobutamine or by inhibiting cAMP breakdown e.g. phosphodiesterase-3 inhibitors (e.g. milrinone). While the calcium sensitizer, Levosimendan's mechanism of action is independent of cAMP, acting by increasing the sensitivity of the cardiomycocytes to intracellular calcium and is an ATP-sensitive K+ channel activator. Inotropes can improve the heart failure patients' haemodynamics in the short-term, but are associated in the mid-to long-term with arrhythmias, myocardial ischemia and increased mortality.

Dobutamine is a synthetic sympathomimetic agent acting primarily on the β1-receptors and a lesser extent on β2-receptors, it is administered as a continuous IV infusion. Dobutamine is recommended in the treatment of patients with low cardiac output and substantially reduced blood pressure, provided they are not receiving concomitant β-blocker therapy [54]. Tolerance or tachyphylaxis can occur as β1-receptors are downregulated in chronic heart failure [55]. A systematic review and meta-analysis comparing dobutamine to placebo or standard care reported no improved mortality but there was a suggestion of increased mortality with an odds ratio of 1.47 for dobutamine compared to placebo (ten studies) or standard care (four studies), $p = 0.06$ [56].

Milrinone is often described as an inodilator as it causes positive inotropy and potent arterial and veno vasodilatation, causing a decrease in pulmonary arterial pressure, pulmonary capillary wedge pressure, systemic BP and systemic and pulmonary vascular resistance while increasing cardiac output [57]. It is effective in managing chronic heart failure patients on concomitant β-blockers. In the OPTIME-CHF trial, patients received short, 48 h, i.v. infusion of milrinone or placebo, those receiving milrinone had significantly more episodes of hypotension and arrhythmias than those on placebo, there was no difference in mortality end-points [58]. Sub analysis demonstrated those with non-ischemic HF had a better short- and intermediate-term prognosis than those with ischemic HF [59]. When administered orally, milrinone also showed increased mortality (PROMISE study) [60].

Levosimendan has both inotropic and vasodilator actions, the half-life of its active metabolite OR-1896 results in prolonged hemodynamic effects of at least 1 week [61]. In the LIDO study levosimendan was superior to dobutamine with regards to the primary hemodynamic end-points [62] and in the REVIVE II trial superior to placebo in terms of improvement of symptoms and signs of heart failure [63]; both were not powered for a mortality end-point. There was no difference between levosimendan and dobutamine in the SURVIVE trial in the primary end-point all-cause mortality at 180 days: 26 vs. 28%, $p = 0.40$ [64]. Following a meta-analysis of several small trials with long-term intermittent levosimendan, the expert panel concluded the results of repetitive use of levosimendan in certain patients as encouraging [61].

As most inotrope studies have shown an increase in mortality, long-term continuous inotropic support is a treatment option as a bridge to heart transplantation or mechanical support and for symptomatic relief at the end of life in those patients with end-stage heart failure where no other therapeutic alternatives are available.

Acute Heart Failure (AHF)

Eighty percentage of AHF cases are due to decompensation of chronic HF (either HFrEF or HFpEF). The rest of the cases constitute the first presentation of the HF syndrome (de novo HF). The development of decompensation can be slow over days or weeks (worsening peripheral oedema) or rapid (pulmonary oedema secondary to an acute coronary event).

A very useful tool for risk stratification of AHF is the modified Forrester classification, which separates the patients in four categories [1]:

- warm and dry (normal perfusion—no congestion)
- warm and wet (normal perfusion—pulmonary congestion)
- cold and dry (hypoperfusion—no congestion)
- cold and wet (hypoperfusion—pulmonary congestion)

The in-hospital mortality of warm and dry AHF patients is low, whereas it is very high in AHF patients who are cold and wet. The above classification also helps guide the pharmacological treatment. Wet patients will require high dose of diuretics (usually given intravenously) to achieve symptomatic improvement. The subgroup of wet patients who have normal or elevated blood pressure also benefit from intravenous vasodilators (nitrates). Cold AHF patients may require inotropes or mechanical circulatory support as part of their management (see relevant chapters). More specifically:

- Diuretics usually provide symptomatic relief in most of AHF patients due to the direct vasodilatory effect and the enhances fluid excretion through the kidneys. The ideal dose and mode of administration (bolus or continuous infusion) is not clear. The recent DOSE trial compared the bolus dosing to the continuous infusion and found no differences as far as the primary endpoints of symptom improvement and renal impairment was concerned [65]. In patients with chronic HF the phenomenon of diuretic resistance is very frequent. This necessitates the use of gradually higher dose of diuretics to achieve the same diuretic effect. The addition of a diuretic acting on the distal tubule (thiazide, metolazone) can be beneficial in patients with diuretic resistance.
- Nitrates are very effective in reducing the preload and the afterload, thus increasing the stroke volume [66]. They are used in patients with hypertension and should be avoided if the systolic blood pressure is <110 mmHg.
- Inotropes should be considered in patients with signs of hypoperfusion (see above chapter for details).

It should be noted that significant part of the AHF management is related to the underlying cause of the AHF, which may require specific interventions (i.e. DC cardioversion for a fast tachyarrhythmia).

Conclusion

Heart failure treatment has evolved over the past three decades. However, progress has been consistent only for chronic HFrEF. In acutely decompensated heart failure and HFpEF, none of the treatments tested to date have been definitively proven to improve survival. Blockade of the renin-angiotensin system is a cornerstone of therapy and should be started, along with beta blockers, as soon as the diagnosis of HF is made. Other drugs, including diuretics, aldosterone antagonists, hydralazine, and nitrates, may be added based on symptoms. Ivabradine and combinatorial treatment with sacubitril and valsartan are promising newly approved therapies that will become widespread in the coming years.

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Cardiac Resynchronization Therapy for Heart Failure

66

Mumin R. Noor, Rebecca E. Lane, and Owais Dar

High Yield Facts

- Electromechanical dyssynchrony, as evidenced by a broad QRS complex on an electrocardiogram, is common in heart failure patients and associated with worse outcomes.
- Combined with optimal medical therapy cardiac resynchronisation therapy (CRT) improves survival and quality of life in patients with left ventricular ejection fraction (LVEF) <35% and broad QRS duration >120 ms.
- Up to 30% of eligible patients fail to respond to CRT therapy.
- The predictors of response to CRT include left bundle branch block (LBBB), non-ischemic cardiomyopathy and female sex.
- The future of CRT involves research directed at expanding the pool of patients who may derive benefit from this technology.
- The combination of CRT pacing with a backup implantable cardiac defibrillator (CRT-D) protects against life-threatening arrhythmias and leads to a survival benefit from all-cause death in some groups of heart failure patients eligible for CRT.

Introduction

The European Society of Cardiology defines heart failure as "a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral edema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/ or elevated intracardiac pressures at rest or during stress" [1].

Epidemiological studies within both Europe and USA quote an incidence of heart failure between 1–5 cases per 1000 population per year [2]. This amounts to approximately 63,000 new cases a year in the UK and 550 000 new cases a year in the USA. The average age at the time of diagnosis is 74 years. Around 1–2% of the population in Europe and USA are living with heart failure at any given moment.

The four most common causes of heart failure within the developed world are ischemic heart disease, hypertension, idiopathic dilated cardiomyopathy and valvular heart disease [3]. From the time of diagnosis, 30% of patients are expected to die within 1 year and 70% within 5 years [4]. Heart failure of all etiologies is associated with a poorer quality of life than many common chronic illnesses such as chronic obstructive pulmonary disease and arthritis [5].

Over the last two decades, enormous progress has been made in the development of both pharmacotherapy and device therapy for chronic heart failure. Large, randomized controlled trials of these medicines and devices have shown improvements in mortality and quality of life for patients with heart failure and reduced systolic function. Limited advances have been made in the treatment of heart failure with preserved systolic function [1].

This chapter will provide the reader with an overview of one of these heart failure device therapies known as cardiac resynchronization therapy (CRT). Key studies, patient selection, implantation techniques and complications will be discussed.

What Is CRT?

CRT (often also referred to as biventricular pacing) involves simultaneous pacing of the right ventricle (RV), the left ventricle (LV), and in most cases the right atrium (RA). This is in contrast to dual chamber pacing in which the RV and RA alone are paced. In CRT conventional endocardial RV and

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RA leads are implanted (as found in any dual chamber permanent pacemaker system). In addition a lead is positioned in one of the branch veins of the coronary sinus (CS). The branch veins of the CS provide access for LV pacing.

How Does CRT Work?

Around a third of patients with heart failure have evidence of electrical dyssynchrony which manifests as a broad QRS complex (>120 ms) on the ECG, typically left bundle branch block (LBBB) [6]. In LBBB the LV depolarises a lot later than usual resulting in the uncoupling of LV and RV function (i.e. mechanical dyssynchrony). The goal of CRT is to restore mechanical synchrony by electrically activating the heart in a synchronized manner. The hemodynamic benefits of CRT include lower LV end-systolic volume, optimised atrioventricular delay, decreased mitral regurgitation and improved diastolic filling time (Fig. 66.1) [7]. One of the main mechanisms of action of CRT is to aid reverse remodelling over time [1].

CRT Trials

The first case series demonstrating the benefits of biventricular pacing were published in the 1990s. In 2001 the Multisite Stimulation in Cardiomyopathy (MUSTIC) trial was the first multi-centre, randomized trial to demonstrate clinical benefits of CRT. This trial included 67 patients who had CRT pacemakers, with LV ejection fraction (LVEF) ≤35%, NYHA class III heart failure symptoms, sinus rhythm and QRS duration >150 ms. The pacemakers were initially programmed to provide backup pacing only. After 3 months the pacemakers were reprogrammed to provide CRT. CRT resulted in significant improvement in 6-minute walk distance, quality of life and peak oxygen uptake as well as decreased hospitalizations [8]. These findings were later confirmed in 2002 by a larger study called The Multicentre InSync Randomised Clinical Evaluation (MIRACLE) trial [9]. In 2004 the COMPANION trial and later in 2005 the CARE-HF trial confirmed that CRT was also associated with a significant survival and quality of life benefit above best medical therapy and independent of implantable defibrillators [10, 11]. More recent trials such as REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE) trial, Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT) trial, and Resynchronization for Ambulatory Heart Failure Trial (RAFT) trial, have shown that CRT benefits patients with LVEF <35%, broad QRS duration and milder symptoms of heart failure (i.e. NYHA II) [12–14].

Indications and Patient Selection

Despite the trial evidence supporting the use of CRT up to 30% of patients do not respond. In general, patients with ischemic etiology and non-LBBB conduction delay are less likely to respond. Patients with severely dilated LV and those

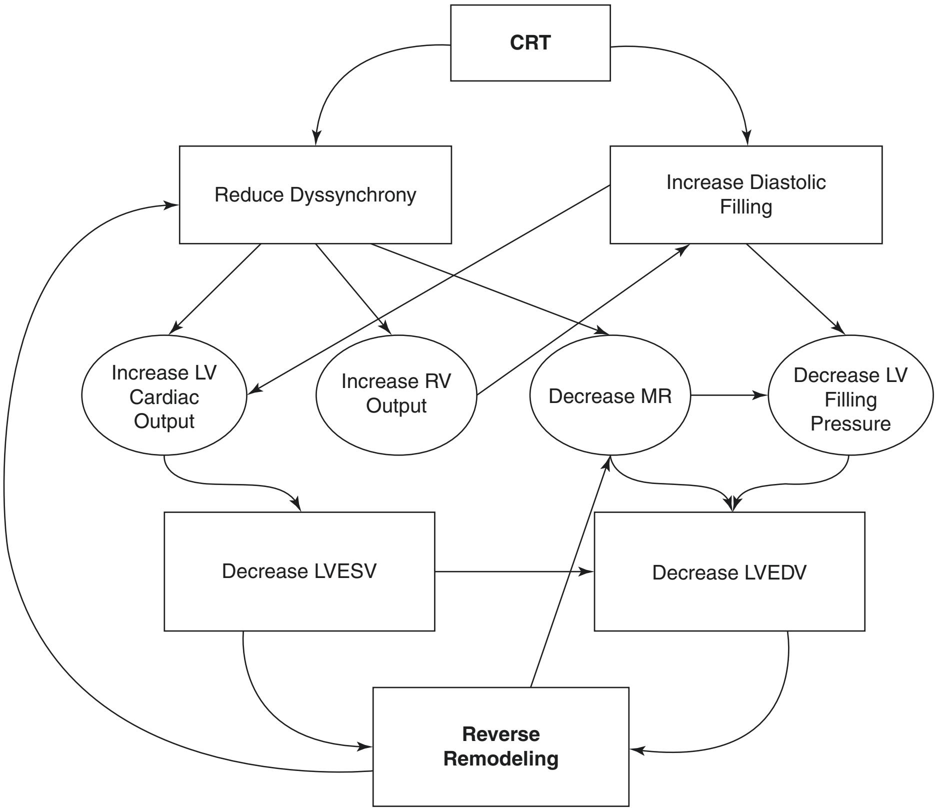

Fig. 66.1 Mechanism of benefit of cardiac resynchronization therapy (CRT). CRT leads to improved intraventricular and interventricular synchrony, as well as an increase in diastolic filling time. These changes improve both systolic and diastolic function of the heart that in turn leads to a decrease in systolic and diastolic left ventricle (LV) volume. Over time, these hemodynamic changes lead to long-standing improvements known as reverse remodeling. Reverse remodeling will additionally improve cardiac synchrony and decrease secondary mitral regurgitation (MR), forming a positive feedback loop. *LA* left atrial, *LVEDV* left ventricle end-diastolic volume, *LVESV* left ventricle end-systolic volume, *RV* right ventricle

with severe mitral regurgitation are also thought less likely to benefit from CRT. Other predictors are listed in Table 66.1. The Echo-CRT trial and a meta-analysis suggest possible harm from CRT when QRS duration is <130 ms. Therefore CRT is not recommended in patients with a normal QRS width [1, 15–17].

Although there are some minor differences in the European and American CRT guidelines overall they recommend CRT in patients with NYHA class II, III, and ambulatory class IV symptoms. Patients must have a left ventricular ejection fraction (LVEF) below 35%, QRS width >120 ms, and be on optimal medical therapy [1, 18]. CRT is not indicated for patients whose comorbidities and/or frailty limit survival with good functional capacity to less than 1 year.

Table 66.1 Features that help to identify CRT responders

Favorable	Less favorable
Left bundle branch block, QRS >150 ms	IVCD, RBBB, QRS <150 ms
Presence of atrioventricular synchrony	Permanent atrial fibrillation
Moderately dilated left ventricle	Massively dilated left ventricle
Mild-to-moderate mitral regurgitation	Severe mitral regurgitation
Nonischemic cardiomyopathy	Ischemic cardiomyopathy with large anteroseptal or posterior scar
Female sex	Male sex

IVCD intraventricular conduction delay, *RBBB* right bundle branch block

Heart failure patients with a LVEF <35% who are likely to RV pace more than 40% of the time are also felt to benefit from CRT pacing since RV pacing is associated with increased dyssynchrony and potentially adverse remodelling [1].

Technical Considerations

The majority of patients undergo CRT with conscious sedation combined with local anesthesia. In selected cases, general anesthesia is required (e.g. patients who are difficult to sedate, thin patient requiring sub-pectoral device placement). The procedure is performed in a cardiac catheterisation laboratory and is considered to be a minimally invasive procedure. The site where the device will be implanted (i.e. the right or left side of the chest wall) is determined mainly by the patient's preference or by the location of a pre-existing device. Similar to a conventional pacemaker, a CRT system consists of a pulse generator (containing the computerised hardware and battery) which is placed subcutaneously in the infraclavicular region, and pacing leads which are wires with electrodes at their tips. In addition to endocardial RV and RA pacing leads that are in conventional pacemaker systems (PPM), CRT systems include an additional coronary sinus (CS) lead for LV pacing (Figure 66.2a). When CRT is combined with ICD (CRT-D), the RV lead contains the defibrillator coil and the pulse generator contains the necessary hardware which is bigger in size when compared to PPM or CRT-P (Fig. 66.2b).

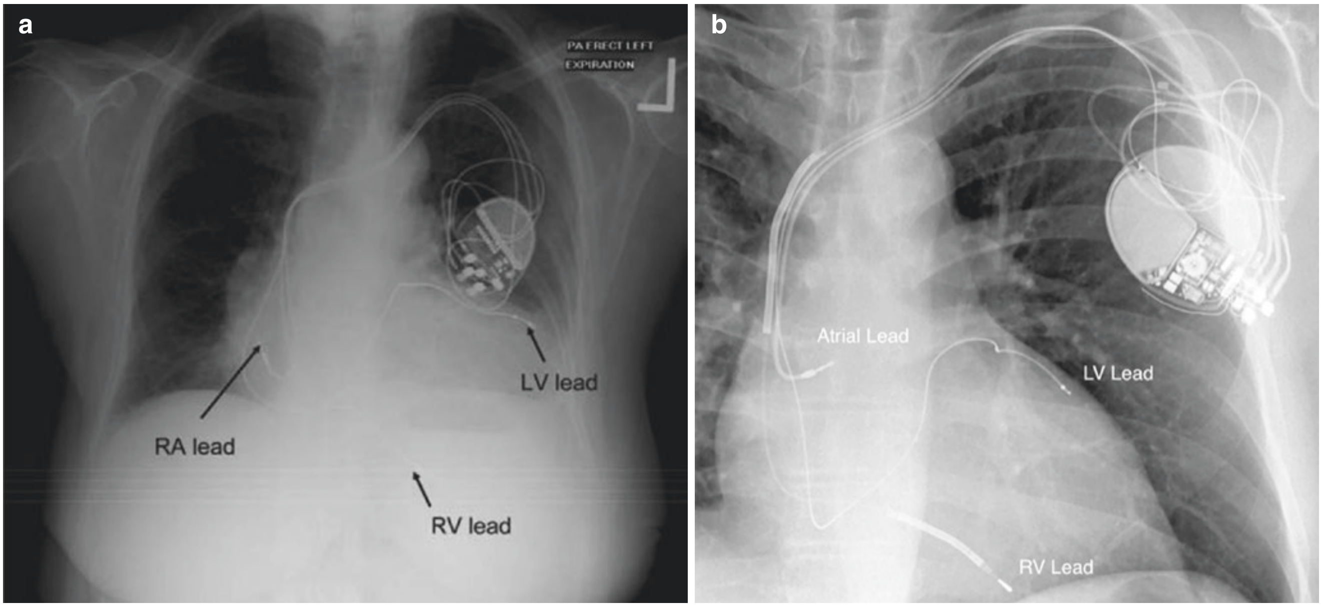

Fig. 66.2 (**a**) Cardiac resynchronisation therapy pacemaker (CRT-P) showing pacing leads in right atrium, right ventricle and in the coronary sinus to pace the left ventricle. (**b**) Cardiac resynchronisation therapy defibrillator (CRT-D) includes built in implantable cardioverter defibrillator. In comparison to CRT-P, note the RV lead contains the defibrillator coil and the pulse generator is bigger containing the necessary hardware. (Republished with permission of Ochsner Clinic Foundation [19])

Venous Access

Access for the RA, RV and LV is achieved via the axillary, subclavian, or cephalic veins. After the puncture is performed, Seldinger technique is used to place splittable sheaths into the subclavian vein. The RV and RA leads are positioned in the RV and RA respectively. In cases with difficult venous access, a contrast injection in the peripheral vein of the arm can be used to visualise the cephalic, axillary and subclavian vein (Fig. 66.3).

Cannulation of the Coronary Sinus

Finding the entrance to the CS is a key step in the placement of an LV lead. The ostium of the CS measures 5–15 mm in diameter and is located on the posterior interatrial septum anterior to the Eustachian ridge and posterior to the tricuspid annulus [20]. Preshaped guiding delivery sheaths are used and are available in different shapes (Fig. 66.4) [21]. The left anterior oblique 30°–45° projection is most commonly used to guide CS access.

Coronary Sinus Venogram

Once the CS is successfully cannulated a balloon catheter is inserted to perform an occlusive CS venography in two projections (LAO and RAO 30°–45°) to facilitate LV lead implantation [22]. The balloon catheter is guided with a percutaneous coronary intervention wire and the balloon catheter is advanced to the end of the guiding delivery sheath under fluoroscopy. Retrograde injection of contrast opacifies all potential target veins, valves, structures, collateral connections and specific anatomic details of the target veins that will help to make the right choice for the LV lead placement (Fig. 66.5). Often long cine sequence is required to visualize collaterals or side branches occluded by the balloon.

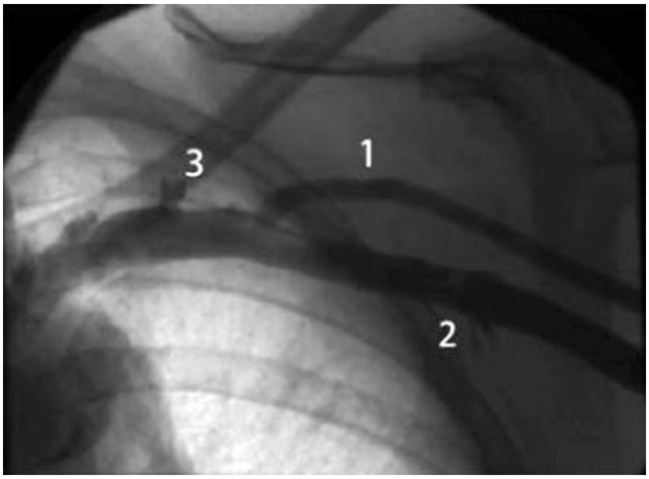

Fig. 66.3 Contrast venogram showing the (1) cephalic, (2) axillary vein and (3) the subclavian vein (Republished with permission of Ochsner Clinic Foundation [19])

LV Lead Position

LV pacing from the lateral, postero-lateral or antero-lateral cardiac vein provides the optimal result of the CRT device [23]. It is not always possible to place the leads in these areas, either because of the lack of appropriate branches overlying the area of dyssynchrony, because of poor capture, or because of diaphragmatic capture. In some of these cases, visualization of the middle cardiac vein can help to find a way to a lateral position for the LV lead.

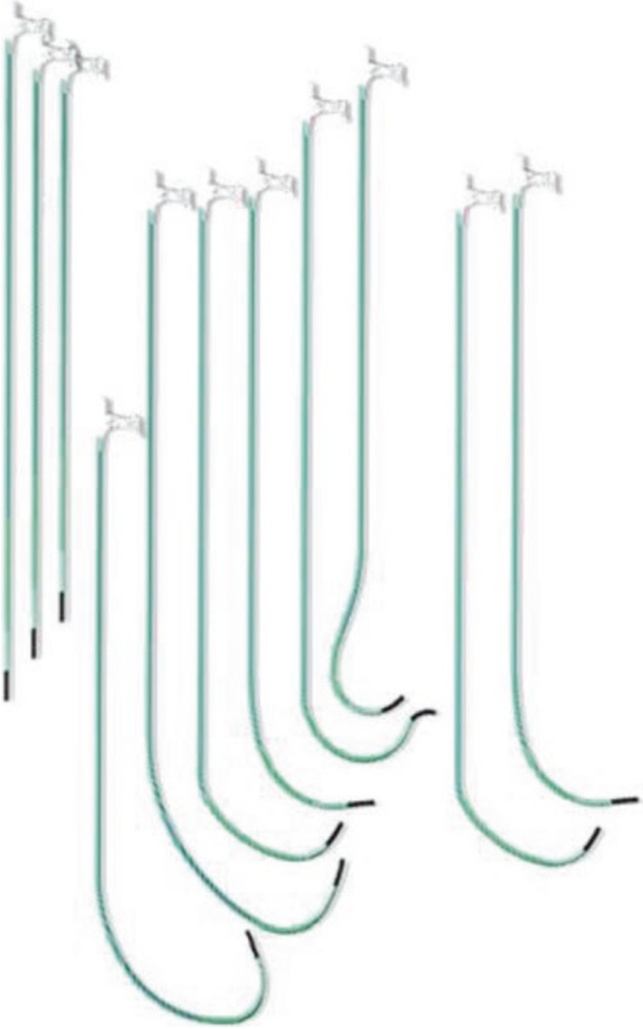

Fig. 66.4 Selection of coronary sinus cannulation catheters

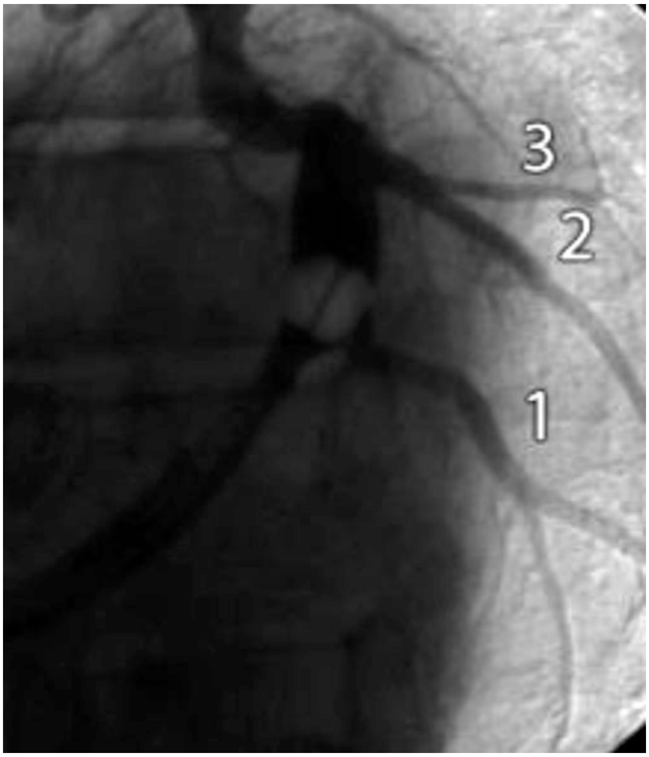

Fig. 66.5 Retrograde coronary sinus venogram in LAO projection. (1) and (2) large postero-lateral branches and (3) a small lateral branch

Post Implantation

Post implantation chest radiography should be performed (in the posteroanterior and lateral views) to detect pneumothorax and to document lead position. This facilitates assessment for possible lead dislodgement if a change in lead parameters should be observed in the future.

Change in the capture threshold or Diaphragmatic capture may be seen soon after implantation as the patient is moved from the procedural table. This occurs because of a change in the anatomic relationship of the heart to the surrounding structures (the diaphragm or the phrenic nerve) or because of a change in lead position. In this situation, adjusting LV lead vectors or the voltage output is often sufficient in avoiding diaphragmatic capture and improving the capture threshold [22].

Device Programming

Aim of device programming is to yield high percentage reliable biventricular pacing with at least 95% of biventricular pacing to benefit from CRT. The atrioventricular (AV) delay should be programmed to be short [24]. Device manufacturers have developed several algorithms that allow automatic programming of AV delay as well as RV to LV delay to optimise biventricular pacing. However, these algorithms have not been associated with improved outcomes. Another option is to use echocardiography-based parameters for AV optimization, although this is not supported by clinical outcome data [25].

Complications

Complications associated with conventional pacing may occur during biventricular pacing. These include infection (localised or systemic), bleeding, hematoma, lead displacement, equipment failure (i.e. fractured pacing wire, faulty pacing box) and pneumothorax.

Complications associated with LV lead placement include LV lead dislodgement (occurs in around 5% of cases) [26], inability to cannulate the CS (between 7.5% and 10%) [12, 13] and CS dissection (2.1%) [27]. CS perforation or rupture is a rare complication but often associated with pericardial effusion. Usually, they are of little consequence because the venous circulation is a low pressure system. However, if pericardial effusion is present, serial echocardiograms should be obtained to evaluate for continuing accumulation or development of tamponade. Peri-implantation mortality risk is reported as 0.4% from ten pooled studies [22].

The Future

The future of CRT involves research directed at expanding the pool of patients who may derive benefit from this technology because even with current patient selection criteria, there remains a sizeable percentage of patients who do not benefit from this therapy.

There is a suggestion that LV pacing at two different CS sites in addition to RV pacing might provide even better resynchronisation and better outcomes [28]. Looking back since the early days of CRT there has been real improvements in lead and generator technology (e.g. quadripolar LV leads have reduced complications with phrenic nerve stimulation and modern generators allow wireless telemonitoring and detection of arrhythmias). It is now possible to pace the LV using leadless pacing systems [29].

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67

Intra-aortic Balloon Pump

Nnamdi Nwaejike and Mani A. Daneshmand

High Yield Facts

- Intra-aortic balloon pump (IABP) support was initially described in 1968 by Kantrowitz et al.
- IABP improves coronary perfusion.
- IABP reduces left ventricular afterload.
- IABP is most effective when it is inserted before it is needed (pre-emptive versus emergency placement).
- Femoral artery placement is easily accessible but confines patients to bed.
- Axillary artery placement allows ambulation.
- IABP is thrombogenic.
- Monitoring for thromboembolism, bleeding, migration, mal-perfusion and cardiac functional recovery is mandatory.
- Decreased urine output after insertion of IABP can occur because of juxta-renal balloon positioning.
- Hemolysis from mechanical damage to red cells can reduce the hematocrit by up to 50%.
- Suboptimal timing of inflation and deflation of the balloon produces hemodynamic instability.

Introduction

The intra-aortic balloon pump (IABP) is a mechanical support device that can improve cardiac function by reducing left ventricular after-load and improving coronary perfusion.

The IABP consists of a double-lumen catheter with an inflatable balloon attached to the distal end. One lumen of the balloon catheter is attached to a pressure-transducer that monitors the patient's arterial pressure; the other lumen which is connected to the inflatable balloon is attached to a helium gas reservoir. When properly placed, the inflatable balloon should lie between the origin of the left subclavian artery and the diaphragm. The IABP console initiates the appropriate timing of IABP inflation by monitoring the arterial and balloon-pressure waveforms as well as the electrocardiogram (ECG).

IABP support was initially described in 1968 by Kantrowitz et al. [1]. The IABP was placed via the femoral artery which is easily accessible. Ten years later an alternative approach by percutaneous insertion into the subclavian artery, due to poor aorto-iliac arteries, was described by Mayer et al. [2]. McBride et al. [3] described an axillary artery insertion, 11 years later, via surgical cut-down and insertion of the IABP directly into the vessel through a purse string with the goal of providing patients the freedom to ambulate.

Mechanism of Action

The IABP is also described as an intra-aortic counterpulsation device. The console is programmed to identify a trigger for balloon inflation and deflation. The most commonly used triggers are the ECG waveform and the systemic arterial pressure waveform.

Balloon inflation causes 'volume displacement' of blood within the aorta, both proximally and distally. This leads to an increase in coronary blood flow and improvements in systemic perfusion by augmentation of the intrinsic 'Windkessel effect', whereby potential energy stored in the aortic root during systole is converted to kinetic energy with the elastic recoil of the aortic root [4].

IABP consoles run algorithms to correlate inflation and deflation of the balloon in opposition to the cardiac cycle.

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The balloon inflates in early diastole displacing blood into the aortic root and coronary arteries thereby improving coronary perfusion and myocardial oxygen supply; it deflates in early systole to reduce ventricular after-load which enhances left ventricular function (Fig. 67.1).

IABP improves the ventricular performance of the failing heart by enabling an increase in myocardial oxygen supply and a decrease in myocardial oxygen demand (Fig. 67.2). The mechanical displacement of blood in the aorta reduces systolic pressure and increases diastolic pressure. The reduction in systolic pressure in the aorta results in reduced end-diastolic pressure (afterload), reduced end-diastolic volume (preload) and reduced wall tension in the left ventricle. The reduced afterload and preload result in increased cardiac output. Increased diastolic pressure in the aorta causes increased coronary blood flow.

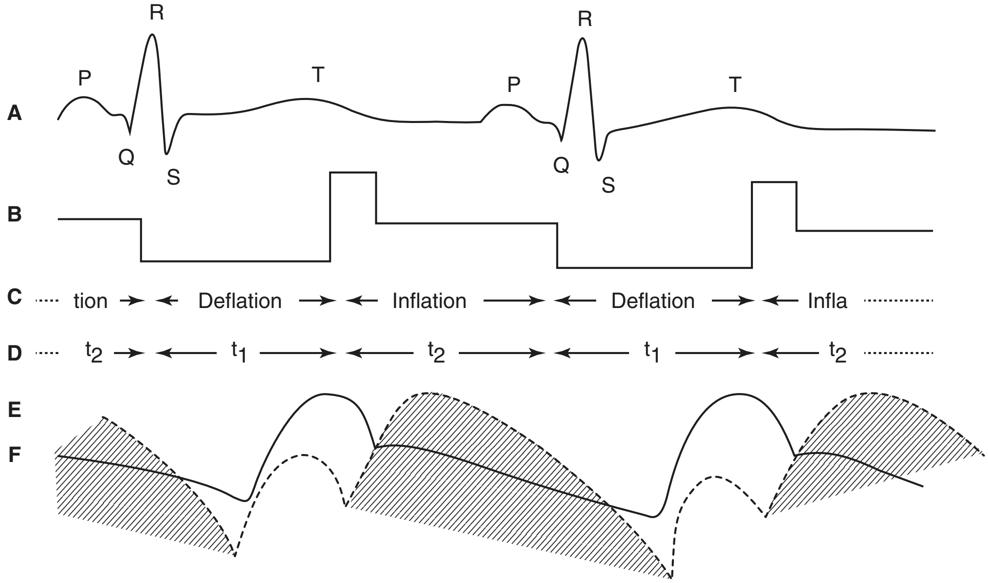
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Fig. 67.1 Haemodynamic function of the balloon. (**A**) ECG. (**B**, **C**) Balloon deflation, corresponding to systole during the cardiac cycle, and inflation, corresponding to diastole. (**D**) Balloon action. (**E**) Aortic pressure curve during balloon function. (**F**) Aortic pressure. (Reproduced from Parissis H, et al. Journal of Cardiothoracic Surgery 2016 **11**:122 under the terms of the Creative Commons Attribution 4.0 International License)

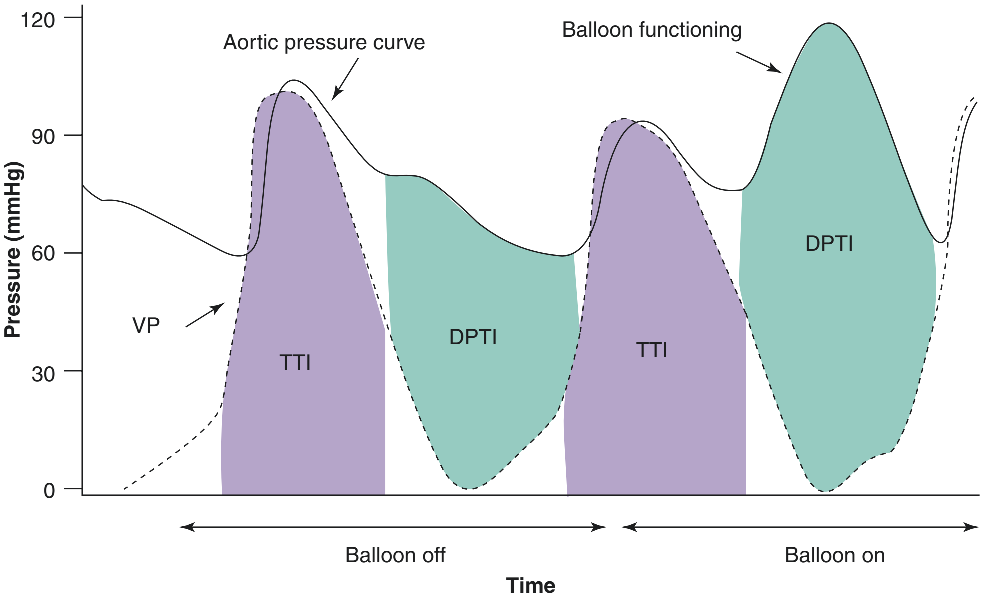

Fig. 67.2 Impact of intra-aortic balloon pump (IABP) on myocardial oxygen supply and demand. Inflation of IABP during diastole increases the pressure difference between aorta and left ventricle (LV), the so-called diastolic pressure time index (DPTI). The hemodynamic consequence of this is an increase in coronary blood flow and, therefore, myocardial oxygen supply. Myocardial oxygen demand is directly related to the area under the LV systolic pressure curve, termed as tension time index (TTI). Balloon deflation during systole causes a reduction in the LV afterload, thereby decreasing TTI. Thus, the ratio of oxygen supply (DPTI) to oxygen demand (TTI), known as the endocardial viability ratio (EVR), should increase if the IABP is working optimally. This can be evidenced by a decrease in coronary sinus lactate. (Reproduced from Parissis H, et al. Journal of Cardiothoracic Surgery2016 11:122 under the terms of the Creative Commons Attribution 4.0 International License)

Table 67.1 Hemodynamic effects of intra-aortic balloon pump therapy

	Increased	Decreased
Aorta	Diastolic pressure	Systolic pressure
Left ventricle		Systolic pressure
		End-diastolic pressure
		Wall tension
		Volume
Heart	Cardiac output	Afterload
		Preload
Blood flow	Coronary blood flow	

Although these effects are predominately associated with enhancement of left ventricular (LV) performance, IABP may also have favourable effects on right ventricular (RV) function by complex mechanisms including accentuation of RV myocardial blood flow, unloading the left ventricle causing reduction in left atrial and pulmonary vascular pressures and RV afterload [4] (Table 67.1). Ntalianis et al. [5] reported on long-term femoral IABP support in 15 patients with biventricular end-stage heart failure (NYHA IV and INTERMACS 1–2) ineligible for alternative LV intervention. Long term IABP support (median 72 days, range 13–115 days) resulted in substantial RV reverse remodeling, decreasing RV end-diastolic dimension and mean right atrial pressure. There was also increased cardiac index, RV stroke work index and peripheral organ function. Mechanisms for these improvements were believed to be improved right coronary perfusion and optimization of septal geometry by relieving LV distension.

Indications for Use

The IABP is widely used for managing cardiogenic shock and augmenting coronary perfusion. However its routine use is controversial. Data from the largest IABP trial to date, the IABP-SHOCK II trial suggested that IABP does not improve mortality in infarct-related cardiogenic shock both in the short-term and long-term [6]; a recent Cochrane review also suggested that IABP does not improve mortality in infarct-related cardiogenic shock [7]. It has on the other hand been suggested that the IABP may be under-utilised as a bridge-to-transplantation [8]. Early (pre-emptive) use of the IABP in cardiac surgery has been shown to be of benefit to patients with severely impaired left ventricular dysfunction, with unstable angina, with critical left main stem disease, in redo surgery, and in off-pump coronary artery bypass surgery [9, 10] (Table 67.2).

Table 67.2 Indications for the use of intra-aortic balloon pump

- Acute myocardial infarction
- Cardiogenic shock
- Refractory unstable angina
- Refractory ventricular arrhythmias
- Acute ischemic mitral regurgitation
- Post-infarction ventricular septal defect
- High-risk percutaneous coronary intervention
- Cardiac surgery
  - Severely impaired left ventricular dysfunction
  - Critical left main stem disease
  - Redo surgery
  - High-risk off-pump coronary artery bypass surgery
  - Weaning from cardiopulmonary bypass
  - Hemodynamic instability

Table 67.3 Contraindications for the use of intra-aortic balloon pump

Absolute	Relative
Aortic regurgitation	Uncontrolled sepsis
Aortic dissection	Abdominal aortic aneurysm
Chronic end-stage heart disease with no anticipation of recovery	Bleeding diathesis
Aortic stents	Severe peripheral vascular disease
	Major aortoiliac reconstruction surgery

We retrospectively compared preemptive (planned) use of the IABP to emergency (unplanned) use in 135 patients (75% male) who underwent cardiac surgery [4]. Planned use was defined as (preoperative AND elective intra-operative) and unplanned use (postoperative AND emergency intra-operative). Predicted preoperative mortality risk was calculated by logistic EuroSCORE. There were no significant differences between the groups with respect to age, preoperative status, operation type, logistic EuroSCORE, or cross-clamp time. The two groups showed a significant difference in mortality: planned IABP insertion, 17%; unplanned insertion, 45% (P = 0.001). A multivariate analysis of the study population showed the logistic EuroSCORE (odds ratio, 0.974; 95% confidence interval, 0.950–0.998; P = 0.035) and timing of IABP use (odds ratio, 4.728; 95% confidence interval, 1.932–11.566; P = 0.001) to be independent predictors of mortality. Preemptive use of the IABP in this patient cohort was associated with a 50% advantage in mortality compared with emergency IABP use. The risk-to-benefit ratio of preemptive IABP use is low in this cohort of patients [9].

Contraindications for Use

The contraindications for IABP use are summarized in Table 67.3. It is contraindicated in patients with aortic regurgitation because it worsens the magnitude of regurgitation. IABP insertion should not be attempted in case of suspected or known aortic dissection because inadvertent balloon placement in the false lumen may result in extension of the dissection or even aortic rupture. Similarly, aortic rupture can occur if IABP is inserted in patients with sizable abdominal aortic aneurysms. Patients with end-stage cardiac disease should not be considered for IABP unless as a bridge to ventricular assist device or cardiac transplantation.

IABP device placement should be avoided in patients with severe peripheral vascular disease. Percutaneous femoral IABP device insertion is contraindicated in the presence of bilateral femoral–popliteal bypass grafts. Uncontrolled sepsis and bleeding diathesis are relative contraindications to the placement of IABP device.

Technique of Insertion and Operation

The IABP device has two major components: (1) a double-lumen 8.0–9.5 French catheter with a 25–50 cc balloon attached at its distal end; and (2) a console with a pump to drive the balloon. The balloon is made of polyethylene and is inflated with gas driven by the pump. Helium is often used because its low density facilitates rapid transfer of gas from console to the balloon. It is also easily absorbed into the blood stream in case of rupture of the balloon.

Before insertion, the appropriate balloon size is selected on the basis of the patient's height (as supplied by Datascope, for a patient <152 cm in height, a balloon volume of 25 cc is appropriate; for height between 152 and 163 cm, balloon volume 34 cc; for height 164–183 cm, balloon volume 40 cc, and for height >183 cm, balloon volume 50 cc). Smaller balloons are available for pediatric use. The diameter of the balloon, when fully expanded, should not exceed 80–90% of the diameter of the patient's descending thoracic aorta.

Femoral Artery Insertion

Percutaneous insertion is by Seldinger method via the right or left common femoral artery. When the tip of the needle is confirmed to be in the lumen of the common femoral artery, the 0.030- or 0.032-in., J-tip guidewire is inserted and advanced through the needle into the descending aorta. This is usually done under fluoroscopic or trans-oesophageal echocardiographic guidance. Once the 7.5-Fr sheath is appropriately positioned, the side port of the sheath is connected to the manifold to record arterial pressure. A 60-mL syringe is connected to the balloon port, and the plunger of the syringe is slowly and completely withdrawn to create a vacuum within the balloon in order to minimise its bulk at insertion. The IABP central lumen is flushed with heparinised saline, and it is advanced over the guide-wire through the arterial sheath under fluoroscopic guidance into the aorta so that the radiopaque marker tip lies about 2 cm below the origin of the left subclavian artery or at the level of the carina, with the distal end above the renal arteries (usually corresponds to L1–L2 vertebrae). There should be no resistance to passing the balloon. Resistance usually indicates aorto-iliac disease, and in this case the balloon should be withdrawn and the aorto-iliac segment reassessed by angiography. Inflation of the balloon in this position should not cause occlusion of either the renal or subclavian arteries. The guide-wire is withdrawn; the central lumen is aspirated and flushed with heparinised saline, and is attached to a pressure transducer. Connections to the IABP console are completed and counterpulsation is initiated.

Axillary Artery Insertion

The feasibility, tolerability, and efficacy of a strategy for trans-axillary artery IABP placement for extended mechanical circulatory support of patients with post-cardiotomy shock as a bridge-to-recovery has been evaluated [11]. IABP is tunnelled through a 6 mm Dacron graft anastomosed to the right axillary artery. The IABP catheter is advanced under fluoroscopic guidance around the aortic arch and placed within the descending thoracic aorta. The trans-axillary access allows for early ambulation of the patient while providing mechanical circulatory assist.

There are several considerations to keep in mind when inserting IABP through axillary artery. Ideal placement requires cut-down and anastomosis of a graft to the axillary or subclavian artery [12] so may not be suitable for emergent settings. In emergent situations, an IABP can be inserted femorally then later converted to axillary in the operating room.

The decision to transition from femoral to axillary IABP is patient-specific. The patient has to show improvement while on femoral IABP e.g. reduced symptoms, improved pulmonary edema, reduced inotropic requirement and improved ventricular function on echocardiography. In short, one should demonstrate the benefit of the femoral IABP before transitioning to the axillary IABP [11].

The IABP orientation is reversed in the axillary approach compared to the femoral artery so the following should be considered: The balloon tip and pressure sensor will sit in the abdomen and the balloon heel will be placed below the SC artery at or just above the level of the carina; care must be taken to avoid having the tip of the balloon curve into an abdominal vessel and cause ischemia; augmentation waves will not look the same as when the pressure sensor tip was at the aortic arch as it will now sense the volume being pushed to the distal aorta rather than the proximal aorta; as the approach requires passage through the subclavian artery, bilateral arterial lines pre-operatively to allow monitoring of both arms may be beneficial [11].

Upper extremity IABP is a minimally invasive and cost-effective strategy that provides haemodynamic support while preserving both the mediastinum and the functional status in bridge-to-recovery (BTR) and bridge-to-transplant (BTT) patients with end-stage heart failure who may not tolerate more invasive modes of mechanical circulatory support.

Table 67.4 Complications associated with intra-aortic balloon pump

Hematological changes, e.g. thrombocytopenia, hemolysis
Transient loss of peripheral pulse
Limb ischaemia
Local vascular injury—false aneurysm, haematoma, bleeding from the wound
Thromboembolism
Aortic dissection
Malpositioning causing cerebral or renal compromise
Compartment syndrome
Infection
Balloon rupture (can cause gas embolus)
Balloon entrapment

While patients may experience higher rates of device exchange and repositioning compared with other modes of mechanical circulatory support, these issues are easily addressed and likely due to the increased mobility allowed by the upper extremity IABP [13].

Complications

Thrombocytopenia is currently the commonest complication occurring in 50% of the patients followed by fever in almost 40% of the cases [14]. Bleeding is also common with aorto-iliac artery injury and dissection. Other recognized but less frequent complications include thromboembolism, distal leg ischemia and balloon entrapment with or without rupture. Despite this, over 70,000 IABP insertions are undertaken annually in the United States alone, with an incidence of between 5% and 10% amongst all patients undergoing cardiac surgery [15]. Complications associated with IABP use are summarized in Table 67.4.

Systemic Anticoagulation

There are no standardized recommendations for anticoagulating patients with IABPs, assuming the IABP is not left in a 1:3 or less augmentation mode for long periods of time [16]. It is likely best practice to individualize antithrombotic therapy on a patient by patient basis [17]. If the patient is considered at risk of thrombosis or if the IABP is planned to be left in weaning mode (1:3 or less augmentation) for greater than approximately 30 min, systemic anticoagulation should be considered. As a rule, the IABP should never be left in stand-by mode (no inflations) unless it is being removed. Nonheparinized animal models have demonstrated clot formations when the balloon remains deflated for greater than 20 min [18]. The basis for anticoagulation is because of the risk of local clot formation around the balloon in the aorta, which could have dire consequences of systemic embolization. Additionally, systemic anticoagulation may potentially decrease the incidence of limb ischemia because of slower blood flow in limb with the IABP sheath [19].

Common Problems and Troubleshooting Measures

Poorly Synchronized Timing

The pressure waveform generated by the IABP can be used to assess the effectiveness of counterpulsation, and to troubleshoot the balloon pump setup. Poorly synchronised balloon inflation and deflation timing can be massively detrimental (or at least unproductive).

However, this whole balloon timing business, generally speaking, is an artefact of a bygone era, when timing was under greater manual control. Automatically timed pumps are the standard today, and many people will never encounter these waveforms in their practice; however one should still be familiar with them.

Early Balloon Inflation

The early inflation of the IABP balloon is a detrimental in every respect, with no upsides (Fig. 67.3). Firstly, as the balloon inflates the left ventricle is still contracting, trying to eject blood through the open aortic valve. Suddenly, it finds itself working against not only the systemic vascular resistance, but also the balloon pressure. Not only that, but some blood will be ejected backwards out of the aorta and into the left ventricle, increasing its volume and putting greater stress on its walls. This corresponds with increased subendocardial oxygen demand.

The diastolic augmentation which was supposed to fill the coronary arteries is wasted. Because the LV is still contracting when the balloon inflates, the subendocardial vessels are squeezed by the contracting myocardial muscle. The resulting increase in coronary vascular resistance results in decreased flow though the coronary circulation. Even though the diastolic augmentation peak is higher, the flow through the coronary circulation is still reduced.

Then, the aortic valve closes prematurely. The duration of systole is reduced, and the stroke volume is reduced; thus for any given heart rate early IABP balloon inflation decreases cardiac output.

Late Balloon Inflation

The balloon is supposed to inflate just as the aortic valve closes. Any later, and much of the enhancement of diastolic blood pressure is lost. The blood that was going to be displaced by the balloon is gone-it has moved on; and the elastic recoil of the aortic walls has been spent.

However, the decrease in diastolic augmentation is not detrimental. The mean diastolic pressure will still be

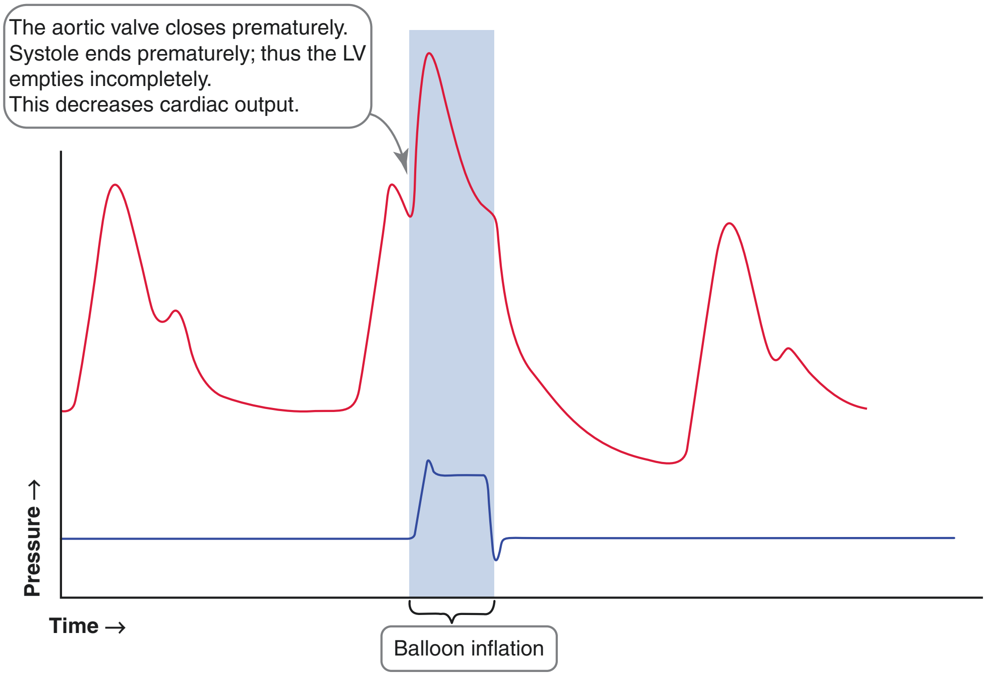

Fig. 67.3 Early inflation of intra-aortic balloon pump. (Reproduced from https://derangedphysiology.com/main/required-reading/cardiothoracic-intensive-care/Chapter%206.3.4.2/pathophysiology-abnormal-iabp-arterial-waveforms under the terms of the Creative Commons Attribution 4.0 International License)

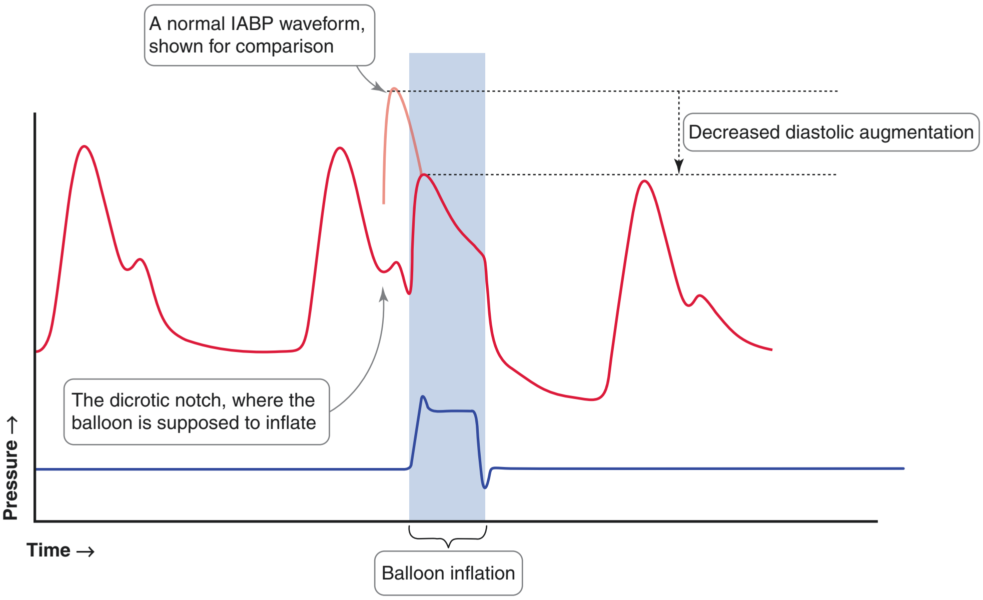

Fig. 67.4 Late inflation of intra-aortic balloon pump. (Reproduced from https://derangedphysiology.com/main/required-reading/cardiothoracic-intensive-care/Chapter%206.3.4.2/pathophysiology-abnormal-iabp-arterial-waveforms under the terms of the Creative Commons Attribution 4.0 International License)

increased, and the coronary arteries may still receive a slightly better blood flow than they would with no balloon activity. The issue is that this diastolic augmentation is not *optimal* (Fig. 67.4).

Early Balloon Deflation

If the balloon deflates too early, the aortic pressure has time to equalise. The aortic end-diastolic pressure reverts to its unassisted level, and there is no reduction in the duration of left ventricular isovolumetric contraction.

Early balloon deflation fails to improve left ventricular afterload**,** and therefore fails to decrease LV oxygen demand. The result of early balloon deflation is a failure to decrease myocardial oxygen demand. There might be still some diastolic augmentation benefit, but the left ventricle is not assisted in opening the aortic valve, and so there is no afterload reduction (Fig. 67.5).

Late Balloon Deflation

Late balloon deflation increases aortic end-diastolic pressure, and thus increases afterload and LV oxygen consumption (Fig. 67.6). There will be a period during which the left ventricle is contracting isovolumetrically against a closed aortic valve, backed by an unnaturally raised aortic end-diastolic pressure. Given that isovolumetric contraction is where 90% of myocardial oxygen is spent, one can see how

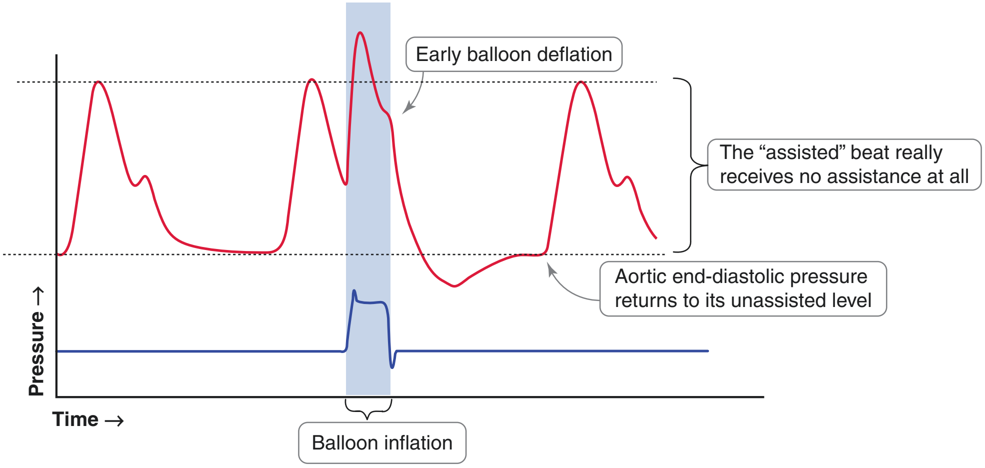

Fig. 67.5 Early deflation of intra-aortic balloon pump. (Reproduced from https://derangedphysiology.com/main/required-reading/cardiothoracic-intensive-care/Chapter%206.3.4.2/pathophysiology-abnormal-iabp-arterial-waveforms under the terms of the Creative Commons Attribution 4.0 International License)

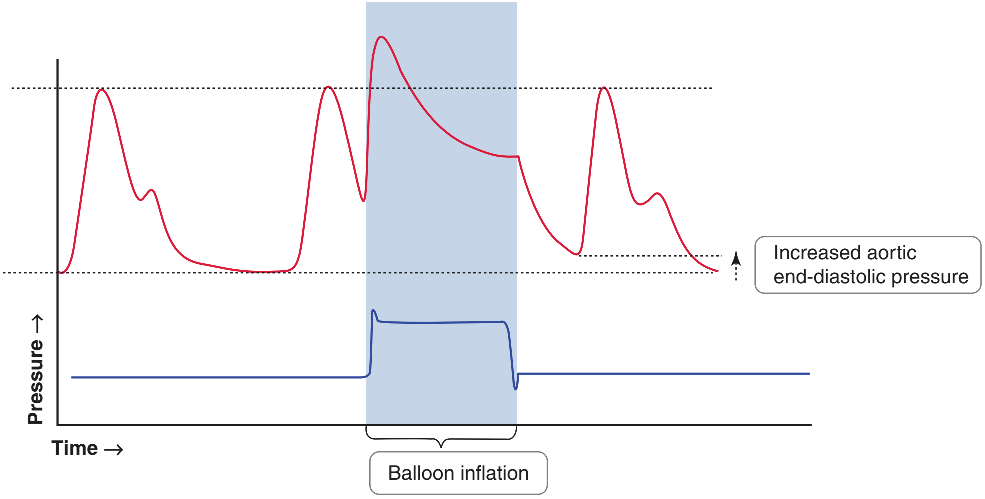

Fig. 67.6 Late deflation of intra-aortic balloon pump. (Reproduced from https://derangedphysiology.com/main/required-reading/cardiothoracic-intensive-care/Chapter%206.3.4.2/pathophysiology-abnormal-iabp-arterial-waveforms under the terms of the Creative Commons Attribution 4.0 International License)

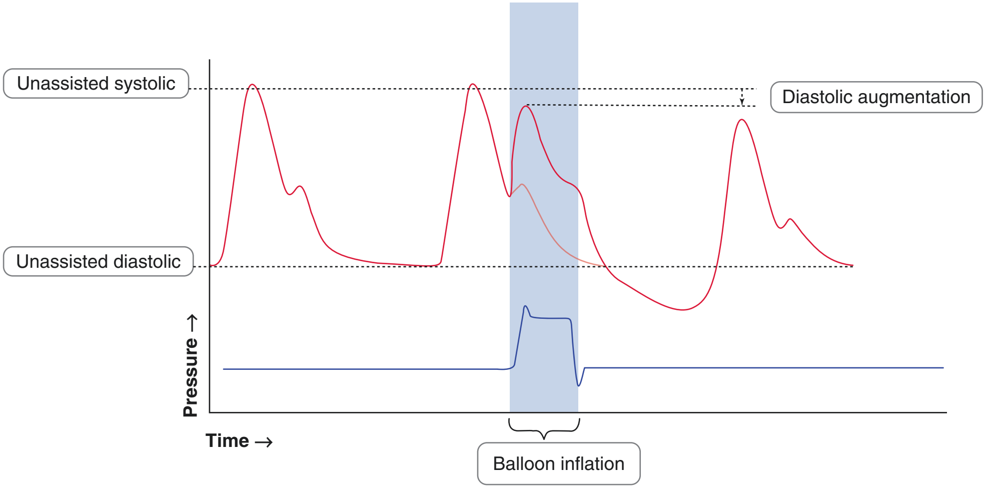

Fig. 67.7 Low diastolic augmentation. (Reproduced from https://derangedphysiology.com/main/required-reading/cardiothoracic-intensive-care/Chapter%206.3.4.2/pathophysiology-abnormal-iabp-arterial-waveforms under the terms of the Creative Commons Attribution 4.0 International License)

this is a disadvantage. Late deflation in an automatically timed pump could be the result of a kink in the catheter. If there is some impedance to helium flow, the balloon will not empty rapidly (even though the timing may be perfect).

Poor Diastolic Augmentation Despite Appropriate Timing

Sometimes, the diastolic augmentation peak is just not very high (Fig. 67.7). The coronary artery filling is perhaps a little

Table 67.5 Causes of poor diastolic augmentation despite proper timing

Very poor cardiac output
Decreased systemic vascular resistance
Balloon could be too small
Balloon positioned too high or too low in the aorta
Drop in helium pressure (i.e. the balloon is filling incompletely)
Balloon is not completely out of its sheath (i.e. the "tail" of the balloon does not get a chance to inflate)
Balloon has not unwrapped fully

bit better with the pump, but clearly it is far from ideal. The causes for this phenomenon are listed in Table 67.5.

Limb Ischemia

With regard to ischemic limb injury, common causes include emboli, dissection, or occlusion during balloon inflation. Patients should routinely be monitored for signs of limb ischemia by pulse palpation as well as end organ ischemia [19]. Adequate patient sedation and analgesia are necessary to minimize the risk of device migration, cannula kinking, or removal of the cannula by the patient. Sheathless balloon insertion in addition to smaller balloon and catheters sizes have been advocated by some experts as a way to help decrease the incidence of vascular related complications particularly in patients at significant risk for developing limb ischemia- or vascular-related complications (diabetes mellitus, peripheral vascular disease) [20, 21].

Console Problems

The common console problems and their management is summarized in Table 67.6.

Table 67.6 Management of common intra-aortic balloon pump console problems

Problem	Management
Augmentation below limit set	Alarm limit set too high
	• Lower alarm limit
	Sudden change in hemodynamics: mean arterial pressure, stroke volume, heart rate
	• Treat accordingly and consider adjusting limit
	• Search for signs of balloon displacement
No trigger	Unable to sense trigger mode
	• Switch to alternative mode (electrocardiography or pressure)
	• Reconnect electrocardiogram leads or pressure cable
IABP disconnected	The IABP extension tubing has been disconnected
	• Reconnect tubing
	• Refill the IAB with gas
	• Restart IABP
Check IAB catheter	Kink in IAB catheter or tubing
	• Relieve any kinks
	IAB remains within sheath
	• Check IAB markings
	Consider withdrawing sheath
	Balloon does not completely unfold
	• Ensure full augmentation is on
	Consider manual inflation and deflation of balloon
Rapid gas loss	Leak within the IAB circuit
	• Check extension tubing
	• Potential hole or leak in IAB
	• Blood in tubing suggests IAB rupture and IAB should be removed
Low helium	Critically low levels of helium. Less than 24 IAB fills remaining
	• Replace cylinder. Make sure yoke is fully tightened
IABP failure	Failure within the IABP console/computer
	• Rule out electrical malfunction or blood in the condensers

IAB intra-aortic balloon, *IABP* intra-aortic balloon pump

Weaning from IABP

As the patient's hemodynamic status improves, weaning the IABP should be considered. Weaning is typically done in a staged fashion (as opposed to abrupt discontinuation) over several hours by gradually decreasing the ratio of augmentation from 1:1 to 1:2 to 1:3, or 1:4. Some devices offer a 1:8 setting; however, this setting likely need not be used as it carries a high risk of thrombosis and adequate weaning information can be gained from 1:3 augmentation. Of note, it is not recommended to remain on settings of 1:3, 1:4, and especially 1:8 for prolonged periods of time (>30 min) because of high risk of catheter thrombosis. In fact, it is advisable to systemically anticoagulate patients who require these settings for a sustained (multiple hours to days) weaning trial [16]. Once in a 1:2 or 1:3 setting for approximately 30 min, data pertaining to cardiac function (mixed venous, echocardiography, cardiac indices, pulmonary capillary occlusion pressure, serum lactate, and urine output) should be monitored and compared with pre-weaning values. Inotropic support may need to be added or increased during weaning. Typically, the systolic blood pressure will increase as support is weaned due to lack of afterload reduction; however, this is not a sensitive parameter for weaning an IABP. If weaning parameter goals are not achieved or the patient demonstrates worsening cardiac function, the IABP can be placed back into a 1:1 augmentation setting and the weaning trial can be repeated when the patient has again shown signs of improvement or perhaps with addition of inotropy [19]. After multiple failed weaning attempts, consideration of another form of ventricular assist device is warranted. If it is determined that the balloon pump can be safely removed, coagulation status (international normalized ratio, partial thromboplastin time, platelet count) should be within normal or near-normal levels prior to removal. Removal of an IABP can have very deleterious results. Approximately, half of all vascular injuries associated with IABP use occur at the time of placement or removal [19]. Hematomas at the site, pseudoaneurysm formation and retroperitoneal bleed can all have dire consequences for these patients. IABP insertion site holding pressure manually should be done with a "no peek" technique for approximately 45 min. Stabilizing pressure devices may be instituted in some centers after manual compression [19]. During this time, it is prudent to monitor lower extremity pulses to ensure circulation is maintained with the compression.

Conclusion

IABP is the most widely used circulatory support device since its introduction by Kantrowitz and colleagues in the1960s. IABP support effectively reduces the left ventricular wall stress and myocardial oxygen demand, increases the coronary perfusion pressure, stroke volume, cardiac output, and ameliorates ischemia, making it a potentially valuable therapy in cardiogenic shock, acute myocardial infarction, as well as high risk percutaneous coronary intervention and cardiac surgery.

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Extracorporeal Life Support in the Adult

68

Adeel Abbasi and Corey E. Ventetuolo

High Yield Facts

- Extracorporeal life support (ECLS) can be used to provide short-term cardiopulmonary support to critically ill patients.
- Veno-venous extracorporeal membrane oxygenation and extracorporeal carbon dioxide removal can be used to support the respiratory system.
- Veno-arterial extracorporeal membrane oxygenation can support hemodynamics, cardiac function, and provide gas exchange.
- Additional configurations may be employed based on the patient's cardiopulmonary needs.
- A basic extracorporeal life support circuit is comprised of cannulas and tubing, a blood pump, an oxygenator and a heat exchanger.
- Vascular access is commonly obtained with extrathoracic percutaneous cannulation of the internal jugular and/or femoral vessels using the Seldinger technique.
- Systemic anticoagulation is typically required to prevent circuit and patient thromboses.
- The most common ECLS complications include bleeding, thrombosis, infection, and distal limb ischemia.

Introduction

The first heart-lung machine was used for human cardiac surgery in 1953. In 1972, Dr. Bartlett successfully used extracorporeal membrane oxygenation (ECMO) outside of the operating room [1]. This ground-breaking work led to the uptake of extracorporeal life support (ECLS) in neonatal and pediatric populations. Technologic innovations, advances in medical management, and the severe acute respiratory distress syndrome (ARDS) that characterized the 2009–2010 influenza A (H1N1) pandemic popularized the use of ECLS in critically ill adults. There are now over 2700 cases of adult ECLS reported annually to the Extracorporeal Life Support Organization (ELSO) registry. Despite advances in care and completion of modern clinical trials, indications and guidelines for the use of ECLS in adults are not firmly established.

Circuit Configurations and Components

The goal of ECLS is to provide gas exchange and oxygen delivery to the tissues. Depending on the circuit configuration, partial-to-complete cardiopulmonary (veno-arterial [VA-ECMO]) or pulmonary (veno-venous [VV-ECMO]) support is possible. The impact of VA- and VV- configurations on hemodynamics and biventricular function are detailed in Table 68.1. A basic circuit is comprised of cannulas and tubing, a blood pump, an oxygenator, and a heat exchanger. Additional tubing (e.g., "in-line" continuous renal replacement therapy) and monitors (e.g., bubble detectors, pressure gauges) can be added. The degree of support provided by the circuit is in large-part dependent on blood flow (as well as patient hemoglobin, inlet hemoglobin saturation, and properties of the membrane lung); targeted flow rates in adults for VA- and VV-ECMO are usually 60–80 cc/kg/min.

Achievable flow rates during ECLS depend directly on the length and inversely on the radius of the cannulas, particularly

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the drainage cannula. Vascular access is usually obtained by extrathoracic percutaneous cannulation using the Seldinger technique; central cannulation or a direct cutdown approach are alternatives [2]. When the femoral artery is cannulated, a small distal perfusion cannula in the superficial femoral artery may be added to ensure perfusion of the lower limb. In traditional VA-ECMO where the arterial or return cannula is positioned to flow retrograde up the aorta, left ventricular afterload is increased and decompression of the left ventricle may be required (Table 68.1). The subclavian and axillary arteries can also be accessed for arterial cannulation but requires an adjunct synthetic graft [3, 4]. Double lumen cannulas for VV-ECMO provide single site internal jugular access, with drainage ports in the vena cava and a return port in the right atrium, which may reduce recirculation and promote patient mobility. Systemic anticoagulation is initiated typically at the time of cannulation to prevent circuit (and patient) thrombosis but can be withheld or reduced for brief periods.

Table 68.1 Key differences between veno-arterial (VA) and veno-venous (VV) extracorporeal membrane oxygenation (ECMO)

	VA-ECMO	VV-ECMO
Flow characteristics	Non-pulsatile, low pulse pressure	Native (patient) pulse pressure
	No recirculation	Recirculation
Direct hemodynamic support	Partial to complete	None
LV effects	Decreased preload	None
	Increased afterload	None
Coronary oxygenation	Native ejection (patient)	Increased
RV effects	Decreased preload	None
	Decreased afterload	None
Pulmonary	Gas exchange	Gas exchange
	Decreased pulmonary blood flow	Increased pulmonary blood flow

LV left ventricle, *RV* right ventricle

In a typical circuit, venous blood is drained out of a major vein, passed through a pump and a membrane lung (or oxygenator), and oxygenated blood (perfusate) is then returned to a major artery (VA-ECMO) or vein (VV-ECMO) (Fig. 68.1). Cannulas may be added to these traditional

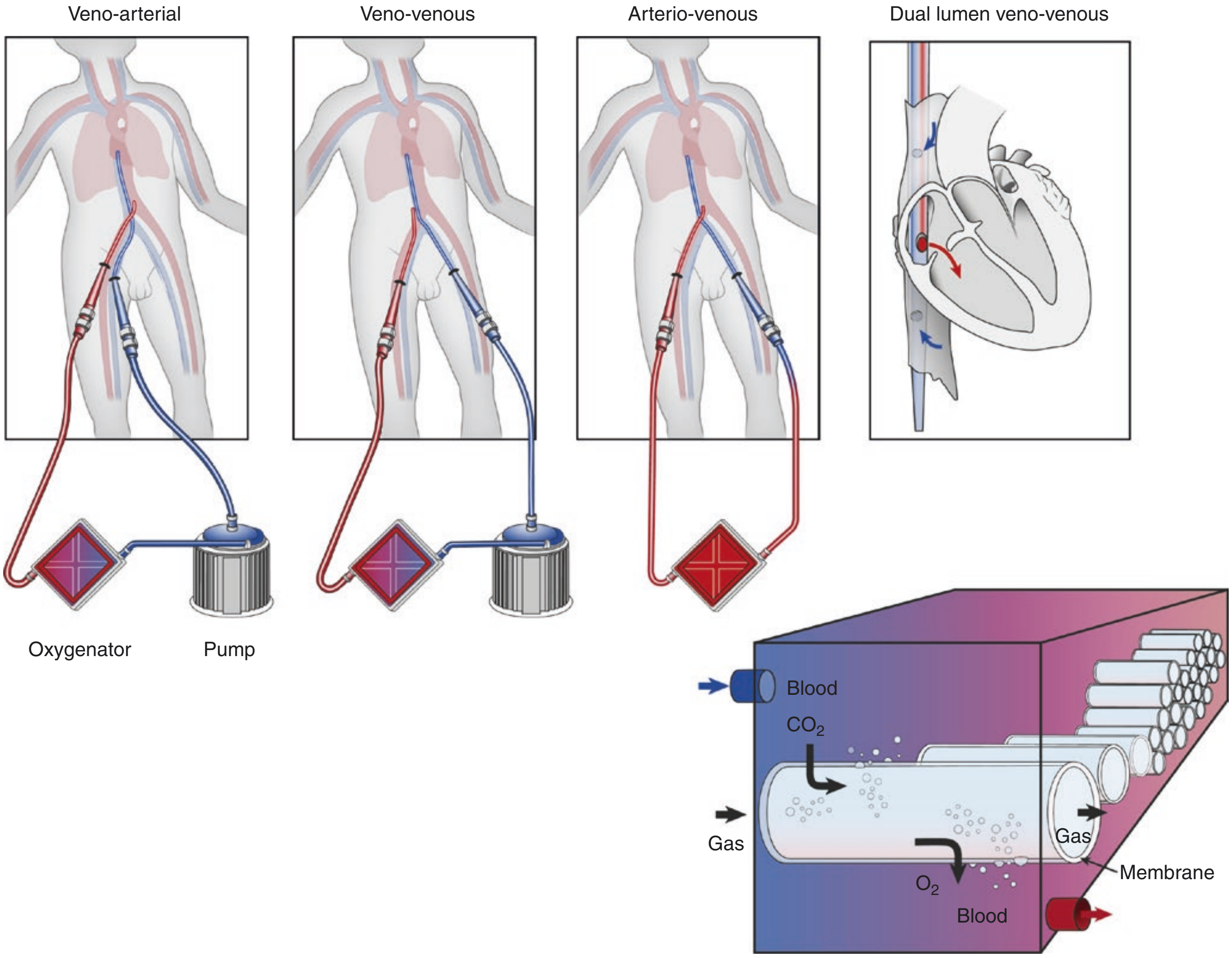

Fig. 68.1 Common extracorporeal life support circuit configurations and schematic of gas exchange in the membrane lung

configurations to provide partial hemodynamic support to a patient with primary respiratory failure (i.e., VVA) or provide gas exchange to a patient with primary cardiac failure (i.e., VAV). Arteriovenous (AV) extracorporeal circuits (with or without pumps) have been used to effectively remove carbon dioxide (CO_2) (extracorporeal carbon dioxide removal [$ECCO_2R$]) and to bypass the right ventricle in a pulmonary artery-left atrial configuration for patients with advanced pulmonary hypertension and right heart failure as a bridge to thoracic organ transplantation [5].

Centrifugal pumps are now used nearly exclusively to support adult ECMO patients. A pressure differential is generated across the pump head via spinning pump components and centrifugal force—this creates negative pressure in the drainage tubing and subsequent blood flow. Modern pumps utilize magnetically driven or magnetically suspended impellers which spin at the desired revolutions per minute to create blood flow, while minimizing heat generation and blood-surface contact and therefore hemolysis [6, 7].

The oxygenator is responsible for gas exchange which occurs by diffusion. Oxygenation capacity is dependent on the surface area of the compressed microporous membrane, maximized by a hollow fiber design (gas phase inside), and contact with the blood phase. Polymethylpentene fiber devices are better suited for longer term ECLS as compared to earlier generation oxygenators. Fresh gas (or sweep gas), is introduced into the gas phase of the membrane (usually as 100% oxygen, oxygen-ambient air, or oxygen-CO_2 mixtures controlled by a blender) and is adjusted to remove CO_2.

When CO_2 removal is the primary goal, substantially lower flow rates are required. In VA-ECMO mixed venous oxygen saturation (SVO_2) may be monitored from the venous drainage limb and flow rates are adjusted to maintain a typical goal $SVO_2 \approx 70\%$. In VV-ECMO, both the drainage and return cannula are positioned in the venous system, which can lead to recirculation and limit oxygen delivery. Since the lungs sit in series in the VV configuration, expected arterial oxygen saturations are lower because perfusate blood mixes with the patient's own venous return and then traverses the pulmonary circuit. Despite this, adequate oxygen delivery can be maintained provided cardiac output is sufficient.

Respiratory Support

Respiratory support can be considered for hypoxemic and hypercapnic respiratory failure, massive air-leak syndromes, or as a bridge to lung transplantation.

ECLS is perhaps most appealing in its potential to reduce the injurious effects of positive pressure ventilation [8]. A low tidal volume ventilation strategy (LTVV) (low volume-low pressure) improves outcomes in ARDS, however some patients may still require salvage interventions for refractory hypoxemia or severe respiratory acidosis on LTVV [8, 9]. Higher plateau pressures in patients treated with LTVV on ECMO have been associated with death in severe ARDS, suggesting there may be no safe plateau pressure limit and that an aggressive strategy to protect the lungs ("lung rest") may be beneficial [10, 11]. In two studies of ARDS patients including the prospective randomized Xtravent trial, pumpless $ECCO_2R$ (interventional lung assist [iLA], NovaLung, Heilbronn, Germany) and very LTVV to achieve lower plateau pressures, as compared to traditional LTVV, resulted in improved biomarkers of lung injury [12, 13]. A recently completed randomized clinical trial, SUPERNOVA (NCT02282657), will address the question of whether $ECCO_2R$ to achieve very LTVV in ARDS is beneficial.

Hypoxemic Respiratory Failure, Acute Respiratory Distress Syndrome, and Recent Clinical Trials

Early randomized trials of ECMO for adults with severe acute respiratory failure and $ECCO_2R$ for severe ARDS showed no benefit of ECLS; however ventilator strategies, circuit configurations, and technology have evolved substantially since these initial studies [14, 15]. The excess morbidity and mortality from ARDS observed during the H1N1 pandemic prompted an increase in the utilization of ECMO for respiratory failure [16–19]. The Conventional ventilation or ECMO for Severe Adult Respiratory Failure (CESAR) trial randomized 180 adult patients with severe ARDS to conventional mechanical ventilation versus referral to a single ECMO center. There was a significantly higher rate of survival without disability at 6 months in the intervention group. Importantly, only 75% of those referred for ECMO actually received it, 25% were managed successfully with a standardized protocol including LTVV, diuresis, and prone positioning. Additionally, practice in the control arm was not standardized and thus patients referred for ECMO were more likely to receive LTVV for longer periods of time which could have accounted for the differences in outcome [20].

While CESAR demonstrated that care at an ECMO-based center may improve outcomes in ARDS, unanswered questions from this pragmatic trial led to the design of the follow-up ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial. EOLIA is the first international, multicenter randomized clinical trial to compare 60-day mortality in severe ARDS patients treated with early initiation of ECMO and very LTVV versus standardized LTVV [21]. The study design permitted crossover to ECMO for patients in the LTVV group with refractory hypoxemia ($SaO_2 < 80\%$ for more than 6 h or investigator discretion). The trial was terminated early for futility after the fourth interim analysis. There was an 11% absolute reduction in 60-day mortality in the ECMO group as compared to the control group which was not significantly different (relative risk 0.76, 95% confidence interval [CI] 0.55–1.04, $p = 0.09$). There was however a significant reduction in the relative risk of treatment failure (defined as death by 60 days in the ECMO group, crossover to ECMO or death in the control group) (relative risk 0.62, 95% CI 0.47–0.82, $p < 0.001$), a predefined key secondary endpoint. It should be noted that there was a high crossover rate (28%), indicating a bias against the control group, although these patients were extremely ill at the time of crossover. Adverse event rates were similar in both arms of the trial. While EOLIA is a negative trial based on the primary end point, it is difficult to draw definitive conclusions given the mixed results and ECMO may still have a role in the management of severe ARDS.

In an adult with hypoxemic respiratory failure, ECLS can be considered when the risk of death exceeds 50% (defined by a $PaO_2/FiO_2 < 150$ mm Hg on $FiO_2 > 0.90$ and/or a Murray Score of 2–3), and is indicated when the expected mortality exceeds 80% (defined by a $PaO_2/FiO_2 < 80$ mm Hg on $FiO_2 > 0.90$ and/or a Murray score ≥ 3) (http://elsonet.org).

Hypercapnic Respiratory Failure and Extracorporeal Carbon Dioxide Removal

Because of the diffusion properties of CO_2, CO_2 clearance is more efficient than oxygenation and depends largely on sweep flow and membrane characteristics, rather than blood flow [22]. In patients who have primarily hypercapnic respiratory failure or in those who require CO_2 removal to achieve LTVV, $ECCO_2R$ may be an appealing strategy because of the lower flow rates (and therefore cannula sizes) that are required to provide "dialysis for the lungs". A number of pilot studies using varied devices in both the VV- and AV- configuration have demonstrated the feasibility of this approach [23–26].

While the use of ECLS and specifically $ECCO_2R$ has not been robustly studied in acute exacerbations of airways disease, it stands to reason that since the primary abnormality is ventilatory failure, the potential for less invasive circuitry and cannulas may reduce complications as compared to VV-ECMO. Several small studies have described the use of $ECCO_2R$ to avoid or replace mechanical ventilation in acute exacerbations of chronic obstructive pulmonary disease (COPD) [23, 24, 27]. The VENT-AVOID trial is an ongoing multicenter open label randomized trial which will compare ventilator free days at day 60 in patients with severe COPD exacerbations randomized to $ECCO_2R$ (Hemolung Respiratory Assist System [Hemolung RAS], ALung, Pittsburgh, United States) versus standard of care noninvasive intubation or mechanical ventilation (NCT03255057).

The use of ECLS for hypercapnic respiratory failure may be considered when the arterial pressure of CO_2 ($PaCO_2$) is > 80 mm Hg or when safe inflation pressures (plateau pressures ≤ 30 cm H_2O) cannot be achieved during an acute airways exacerbation or permissive hypercapnia (http://elsonet.org).

Bridge to Lung Transplantation and Primary Graft Dysfunction

A strategy of "awake ECMO" for patients awaiting lung transplantation offers the theoretical advantage of early mobilization, rehabilitation, and avoidance of endotracheal intubation and its associated complications [28–32]. Both VV- and VA-ECMO have been used to support patients who develop primary graft dysfunction after lung transplantation [33–37] and VA-ECMO has been used in place of traditional cardiopulmonary bypass intra- and post-operatively to control reperfusion and recondition the left ventricle in patients with pulmonary hypertension [38]. To date, there are no controlled studies using ECLS as a bridging strategy in the pre- or post-transplant population.

Cardiac Support

There are no controlled trials comparing short-term mechanical circulatory support devices (i.e., intra-aortic balloon counterpulsation or temporary ventricular assist devices) to VA-ECMO, but ECLS has been shown to be a reasonable salvage strategy in patients with refractory cardiogenic shock of varied etiologies [5, 39, 40]. Failure to wean from intraoperative cardiopulmonary bypass (post-cardiotomy), acute myocardial infarction, ischemic cardiomyopathy, acute myocarditis, and post-partum cardiomyopathy are common indications for VA-ECMO [41]. VA-ECMO has been used to support patients before, during, and after various interventional procedures including percutaneous coronary intervention, valve replacements, and high-risk electrophysiology procedures [42–45]. As compared to other bridging devices used in the catheterization laboratory, ECLS provides gas-exchange support for those patients with oxygenation issues or underlying lung disease and supports right ventricular function in those patients with bi-ventricular failure.

Extracorporeal Cardiopulmonary Resuscitation

Single-center series have reported reasonable survival rates (~30%) to hospital discharge combining extracorporeal cardiopulmonary resuscitation (ECPR) with traditional resuscitation efforts in experienced ECMO centers [46–50]. In general, a patient may be considered an ECPR candidate if the arrest is felt to be of primary cardiac origin and if there has been a failure of return of spontaneous circulation within a prespecified time interval. While there have been no controlled studies, two observational, single-center studies have suggested ECPR confers a survival benefit in adults suffering in-hospital cardiac arrest [49, 51]. In highly experienced centers where ECMO can be deployed in minutes, ECPR may be a reasonable life support modality in highly selected patients.

Relative Contraindications and Complications

There are no absolute contraindications to ECLS and each patient should be evaluated on a case-by-case basis and in the context of a center's experience. ECLS can be associated with a number of complications, including bleeding, thrombosis, infection, distal limb ischemia, and hemorrhagic and ischemic stroke (Table 68.2). The morbidity associated with VA-ECMO for cardiac failure is higher [41]. On-going studies will address best practices for anticoagulation, transfusion, and infection monitoring in ECLS patients (NCT03497338, NCT02895373, NCT02887820, NCT02917486).

Life-limiting comorbidities or additional organ failures that are not considered reversible should be considered relative contraindications. Advanced vascular disease or ease of vascular access may impact a patient's candidacy. Increasing age has been consistently associated with worse outcomes although individual patients of advanced age may be reasonable candidates depending on indication for support and comorbid illness(es) [52–54]. Renal failure has also been repeatedly shown to predict a poor prognosis in patients on VA-ECMO [53–56]. Longer duration of mechanical ventilation prior to ECMO for respiratory support predicts a poor prognosis (particularly mechanically ventilation > 7 days) [57–60]. Both the CESAR and EOLIA trials excluded patients on mechanical ventilation > 7 days prior to study entry [20, 21]. Risk scores which incorporate patient variables and clinical parameters have been developed for predicting survival after the use of VV-ECMO for ARDS and VA-ECMO for refractory cardiogenic shock [61, 62].

In addition to patient-related complications, equipment-related failures can occur [52]. Bi-caval dual lumen catheters must be placed under direct visualization using either fluoroscopic or echocardiographic guidance, as major vessel injury and right ventricular rupture have been reported [63, 64].

Table 68.2 Selected patient-related complications of ECLS as reported to the Extracorporeal Life Support Organization registry, by cardiac versus respiratory indication

	Cardiac	Respiratory
Hemorrhagic complications (%)		
Gastrointestinal	4	4
Cannula site	13	7
Surgical site	13	6
Hemolysis	4	5
DIC	2	2
CNS complications (%)		
Infarct[a]	3	2
Hemorrhage[a]	2	2
Pulmonary complications (%)		
Pneumothorax requiring treatment	2	4
Pulmonary hemorrhage	2	3
Infectious disease complications (%)		
Culture-proven infection	8	12
Musculoskeletal complications (%)		
Limb ischemia	5	2
Compartment syndrome	2	<1
Fasciotomy	3	<1
Amputation	<1	<1

CNS central nervous system, *DIC* disseminated intravascular coagulation, *ECLS* extracorporeal life support

[a] As detected by ultrasound or computed tomography

Long-Term Outcomes

Little is known about the long-term sequelae of ECLS. In the absence of randomized trials with comparable control groups, it is difficult to distinguish morbidity related to critical illness from complications related to ECLS itself. Longitudinal data from the CESAR trial demonstrated no difference in validated surveys of health status, respiratory symptoms, or spirometric measures by treatment allocation at 6 months [20].

Conclusion

ECLS is being increasingly used to support critically ill adults with refractory cardiopulmonary failure. The pioneering work of well-established centers, technologic advances in circuit components, and the experience gained in the H1N1 pandemic and modern-day clinical trials have allowed for the successful rescue of many patients, but significant questions remain regarding the appropriate patient population, optimal medical and surgical management techniques, outcomes, and cost effectiveness.

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Temporary Circulatory Support Devices

69

Gerin R. Stevens and Brian Lima

High Yield Facts

- Temporary mechanical circulatory support (MCS) devices are used for patients in refractory cardiogenic shock, in high risk interventions, as bridging therapy to advanced durable support, to unload the left ventricle (LV) during veno-arterial extracorporeal membrane oxygenation, or for isolated right ventricle (RV) failure.
- The Impella® devices are all impeller-driven, axial flow pumps that are placed percutaneously or surgically (using a cut-down or direct implantation) to assist the LV, RV or both ("Bipella").
- The Impella® 5.0 affords "full" systemic circulatory support by delivering up to 5 L/min of flow.
- TandemHeart™ is an extracorporeal, left atrium (LA) to femoral artery (FA) bypass circuit that works in parallel (i.e., "tandem") with the native ventricle and can be used for LV or RV failure
- The CentriMag™ is an extracorporeal, centrifugal pump capable of delivering up to 10 L/min of flow, employing a magnetically levitated rotor without any bearings, seals, or shafts.
- Bleeding, vascular complications, infection, thromboembolism and air embolism are the common complications associated with the use of temporary MCS devices.
- The development of a "shock team" that is inclusive of interventional and heart failure cardiologists as well as a transplant/VAD cardiac surgeon is imperative to select the right device for the right patient at the right time and with the right exit strategy.

Introduction

The use of temporary mechanical circulatory support (MCS) devices, placed either peripherally or centrally, has expanded over the last decade to include use during high-risk percutaneous coronary intervention (PCI) or ablation procedures and to support patients in cardiogenic shock. The choice of device to implant depends upon the anticipated duration of support, the need for uni- or biventricular support, the potential for recovery and candidacy for a fully implantable left ventricular assist device (VAD) and/or cardiac transplantation. Typically, these are devices used from hours to days or weeks, depending upon the clinical scenario.

The selection of a temporary MCS device has rapidly expanded from the early use of the intra-aortic balloon pump (IABP) to percutaneous VADs (pVAD) that can be rapidly deployed by the interventional cardiologist or cardiac surgeon and offer strategies for uni- or biventricular support. In addition, many centers capable of offering advanced heart failure expertise are moving towards formalized extracorporeal membrane oxygenation (ECMO) programs, for both cardiopulmonary (veno-arterial, VA) and pulmonary (veno-venous, VV) support.

This chapter will provide an overview of temporary MCS devices, including Impella® (Abiomed, Danvers, MA, USA), TandemHeart™ (CardiacAssist, Inc. dba TandemLife, Pittsburgh, PA), and CentriMag™ (Abbott Labs, Lake Bluff, IL, USA), describing advantages as well as adverse events associated with each strategy. The use of IABP (Chap. 67) and ECMO (Chap. 68) are addressed elsewhere in this book.

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Table 69.1 Indications for temporary mechanical circulatory support

Cardiogenic shock due to:
Acute myocardial infarction
Decompensated systolic heart failure
Acute myocarditis
Post-cardiotomy shock
Acute rejection post-cardiac transplant
High-risk interventions
Percutaneous coronary intervention
Ventricular tachycardia ablation
Bridge to decision, durable VAD or cardiac transplant
Right ventricular failure
Left ventricular unloading for veno-arterial ECMO

Adapted from Gilotra and Stevens [35]
ECMO extracorporeal membrane oxygenation, *VAD* ventricular assist device

Indications for Temporary MCS

The indications for temporary MCS are outlined in Table 69.1. In general, they are used for patients in refractory cardiogenic shock arising from a variety of causes, including acute myocardial infarction (MI), acute myocarditis, decompensated systolic heart failure, post-cardiotomy shock, and acute rejection post-cardiac transplant. Increasingly, these modalities have also been employed in high risk interventions, as bridging therapy to advanced durable support, to unload the left ventricle (LV) during VA-ECMO, or for isolated right ventricle (RV) failure.

Cardiogenic shock is characterized by pump failure resulting in low cardiac index (i.e., < 2.2 L/min), high preload (i.e., PCW > 15), and evidence of systemic hypoperfusion (i.e., oliguria, altered mental status, cool extremities) and/or an elevated serum lactate level [1]. Several studies also include a systolic blood pressure (SBP) <90 mmHg or ongoing catecholamine support to maintain SBP > 90 plus signs of hypoperfusion [2, 3]. In a 30-year population-based study, in-hospital and 30-day mortality for patients with cardiogenic shock from acute MI has declined since the 1970s (76.1% versus 45.4% and 20.7% versus 12.8%, respectively), however survival in the current era remains poor [2, 4].

Patient Selection

While the indications for the use of temporary circulatory support may be clear, patient selection can be more difficult. Patients often present in extremis and are not known by the implanting center. There may be little or no information about comorbidities and the neurologic status may be unclear. Careful consideration of known factors, such as age and presentation, should be reviewed quickly by a multidisciplinary "shock team," including the interventional and heart failure cardiologists and the cardiac surgeon, so that device selection and exit strategy are discussed. The ideal candidate for temporary support is one without any clear contraindications for durable LVAD or cardiac transplant if there is no myocardial recovery. However, a pre-defined endpoint should be considered in the event that the initial strategy is not successful and definitive therapy cannot be offered.

Options for Temporary MCS

Impella®

The Impella® devices are all impeller-driven, axial flow pumps that are placed percutaneously or surgically (using a cut-down or direct implantation) to assist the LV, RV or both ("Bipella"). Each requires that the patient tolerate systemic anticoagulation with an activated clotting time (ACT) of 160–180 s [5]. The range of devices includes the Impella® 2.5, CP, 5.0, LD, and RP (Fig. 69.1) with maximal flows ranging from 2.5 to 5.0 L/min (Table 69.2). Possible complications (Table 69.3) include bleeding, vascular injury, leg ischemia, pump migration and hemolysis [6, 7].

Early studies of the Impella® 2.5 demonstrated safety and feasibility of the device in patients with severe systolic impairment requiring high risk PCI, but failed to show a difference in 30-day major adverse cardiovascular events (MACE) compared to IABP for periprocedural support [6, 8]. In cardiogenic shock due to acute MI, the Impella® 2.5 group had a significant increase in cardiac index after 30 min versus IABP, but no difference after 4 h or in 30-day mortality rates at the expense of requiring more blood products in the Impella group (ISAR-SHOCK) [9]. Similar results were seen in the Impella-EUROSHOCK-Registry, which retrospectively found very high overall 30-day mortality (64.2%) [10]. And, despite higher flow rates, the Impella® CP failed to show a difference in 30-day or 6-month mortality rates after acute MI when compared to IABP [11].

Interestingly, differences are seen with early implantation of the Impella® 2.5 or CP prior to PCI and before the need for inotropes and vasopressors. In 287 consecutive patients enrolled in the catheter-based VAD (cVAD) registry, survival was 66% when Impella® support was initiated <1.25 h from shock onset, but dropped to 37% if within 1.25–4.25 h, and 26% if >4.25 h [4]. An analysis of 15,259 patients from the same registry found a 59% survival rate versus 52% when the Impella® was used as the initial support strategy, 63% versus 49% for those with invasive hemodynamic monitoring, and 56% versus 51% in a center with higher implantation volume (≥7 year^{-1}) [12]. Evidence may also suggest that primary unloading of the LV prior to reperfusion is cardioprotective with a reduction in infarct size and improvement in cardiac function in a swine model of acute MI [13, 14]. The Door to Unloading with IMPELLA CP System in Acute Myocardial

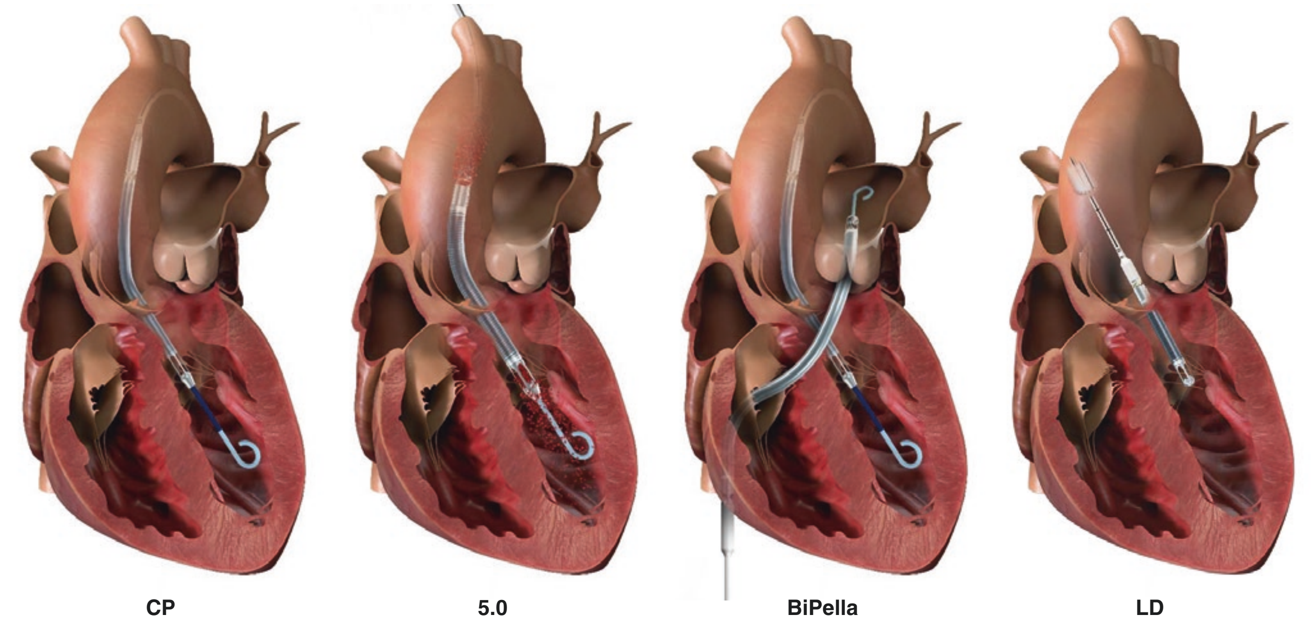


Fig. 69.1 Graphical depictions of the Impella CP, 5.0, BiPella, and LD. The CP is placed retrograde via the femoral artery into the LV. The 5.0 is typically placed via the axillary artery into the LV. Note that the BiPella configuration has both a CP in the LV and the RP implanted via the femoral vein into the pulmonary artery. The LD is implanted through a graft that is sewn to the ascending aorta. The Impella 2.5 is not shown, but is similar to and smaller than the CP. *LV* left ventricle. (Printed with permission from Abiomed, ©2018 Abiomed, Inc.)

Table 69.2 Comparison of temporary mechanical circulatory support devices

Device	Catheter diameter	Mode of access and site	Maximal flow
Impella 2.5	9 Fr/12 Fr*	Percutaneous, FA	2.5 LPM
Impella CP	9 Fr/14 Fr*	Percutaneous, FA	3.5–4.3 LPM
Impella 5.0	9 Fr/21 Fr*	Arterial cut down, FA or AxA	5.0 LPM
Impella LD	Surgical graft	Open chest, Ascending Aorta	5.0 LPM
Impella RP	11 Fr/22 Fr	Percutaneous, FV	4.0 LPM
TandemHeart	21 Fr (FV) and 15- to 19-Fr (FA)	Percutaneous, FV and FA	3.5–5.0 LPM
Tandem Protek Duo	29 or 31 Fr	Percutaneous, RIJ vein	5.0 LPM
Centrimag	Surgical graft	Open chest, LA or LV and/or RA	9.9 LPM

AxA axillary artery, *FA* femoral artery, *FV* femoral vein, *Fr* French, *LPM* liters per minute, *IVC* inferior vena cava, *LA* left atrium, *PA* pulmonary artery, *RA* right atrium, *RIJ* right internal jugular

*Implanted motor diameter

Infarction (DTU) study (ClinicalTrials.gov NCT03000270) has completed enrollment of 50 subjects in the United States and may provide an answer to this question.

The highest flow device in this family, the Impella® 5.0, affords "full" systemic circulatory support by delivering up to 5 L/min of flow. The pump itself is 21 French (Fr) mounted on a 9 Fr catheter. Insertion necessitates surgical placement via cut down onto the femoral artery or axillary artery side graft (10 mm). Axillary artery insertion facilitates patient mobility and transition to more durable therapies. Specifically, the Impella® 5.0 can serve as an effective diagnostic and therapeutic platform that can bridge patients to the most appropriate definitive therapy, such as heart transplant or durable LVAD implantation. The recently published and largest single center experience with Impella® 5.0 as a bridge to decision strategy included 40 patients that were primarily INTERMACS 1 (32%) or 2 (66%), supported for a median duration of 7 days [15]. Of these, 75% survived to "next" therapy, including either transplant or LVAD. A more recent analysis included cohorts from 3 centers totaling 58 patients and similar survival rates (67%) to next therapy were observed [16]. Importantly, 1-year survival was 65% for patients treated with implantable LVAD and 87% for those that underwent transplant.

For support of the RV, the Impella® RP directly bypasses the RV displacing blood from the inferior vena cava into the main pulmonary artery. It is inserted via the right femoral vein under fluoroscopic guidance. A retrospective cohort of 18 patients demonstrated immediate hemodynamic improvement in central venous pressure and cardiac index with a 30-day post-explant survival of 72% [17]. The RECOVER RIGHT study prospectively enrolled 30 patients with RV failure after LVAD, MI, or cardiotomy demonstrating an immediate improvement in hemodynamics and an overall 30-day post-explant survival of 73.3% [18]. While both bleeding and hemolysis were observed, there were no described thromboembolic events and very few had either

Table 69.3 Advantages and disadvantages of temporary mechanical circulatory support devices

Device	Advantages	Disadvantages	Contraindications	Complications
All	Minimal need for specialized support	Need for anticoagulation	Severe peripheral vascular disease Irreversible neurologic disease Inability to tolerate anticoagulation Sepsis*	Bleeding Infection Stroke
Impella®	Peripheral single site insertion Direct ventricular decompression Potential for mobilization Support for days to weeks	Imaging-dependent insertion Need for repositioning Hemolysis No pulmonary support Two devices for biventricular failure	LV thrombus Significant aortic valve disease Mechanical aortic valve Recent stroke Aortic abnormalities	Hemolysis Pump migration Vascular injury Leg ischemia Aortic valve injury Tamponade Ventricular arrhythmia
TandemHeart™	Peripheral insertion Effective ventricular decompression Pulmonary support possible Support for weeks May tolerate less anticoagulation	Imaging-dependent insertion Trans-septal puncture skill set Rigid immobilization Two devices for biventricular failure	Ventricular septal defect Significant aortic insufficiency	Thromboembolism Air embolism Cannula migration Vascular injury Leg ischemia Tamponade Inter-atrial shunt
CentriMag™	Effective ventricular decompression Potential for mobilization Pulmonary support possible Support for weeks to months May tolerate less anticoagulation	Central/surgical insertion Two devices for biventricular failure	Sepsis*	Thromboembolism Air embolism

Adapted from Gilotra and Stevens [35] and Nagpal et al. [36]
*Relative contraindication

tricuspid or pulmonary valve dysfunction. The “BiPella” configuration to support both LV and RV has been mostly case reportable, but a retrospective cohort of 20 patients was recently described. In patients with biventricular failure due to MI, decompensated heart failure, or myocarditis, this percutaneous biventricular approach was feasible and improved hemodynamics, but in-hospital mortality remained 50% in this critically ill group of patients [19].

The Impella® devices have also been used in smaller cohorts for complex ablation procedures. In a prospective, nonrandomized evaluation of patients with LV dysfunction requiring scar ventricular tachycardia (VT) ablation, fewer patients had cerebral desaturation below 55% when supported by the Impella® 2.5 allowing the electrophysiologist longer and safer mapping times [20]. Furthermore, another multicenter, observational study found that patients supported with percutaneous MCS versus IABP allowed for longer VT mapping times and more successful VT ablations [21]. The use of the pVAD for this indication, though, remains limited to a select population of patients in experienced centers.

TandemHeart™

TandemHeart™ is an extracorporeal, left atrium (LA) to femoral artery (FA) bypass circuit that works in parallel (i.e., “tandem”) with the native ventricle and can be used for LV or RV failure (Figure 69.2a). The pump is a centrifugal, continuous flow pump that is placed using fluoroscopic and echocardiographic guidance in the cardiac catheterization laboratory. It was first described in 18 patients with acute MI complicated by cardiogenic shock with an overall mortality rate of 44% [22]. Subsequent studies have shown similar outcomes [23, 24].

For LV support, the 21 Fr inflow cannula is placed via the FV into the LA via trans-septal puncture. Blood is aspirated through a large end hole and 14 side holes into the extracorporeal centrifugal pump and out to the FA. The FA outflow cannula size varies between 15 and 19 Fr, which is the main determinant of output ranging 3.5–5.0 L/min of flow. An external controller regulates the rate of the purge solution, which should be heparinized normal saline, to prevent pump thrombosis. The manufacturer recommended concentration of heparin is 90 units/mL at a fixed rate of 10 mL/h for a goal aPTT of 65–80 s or ACT of 180–220 s. Patients that remain subtherapeutic from the heparinized purge solution alone should have supplemental intravenous heparin infusions to reach the therapeutic target [5].

Several studies have demonstrated a significant improvement in hemodynamic parameters for patients in cardiogenic shock that received the TandemHeart™, but survival remained poor and was influenced by age and indication for

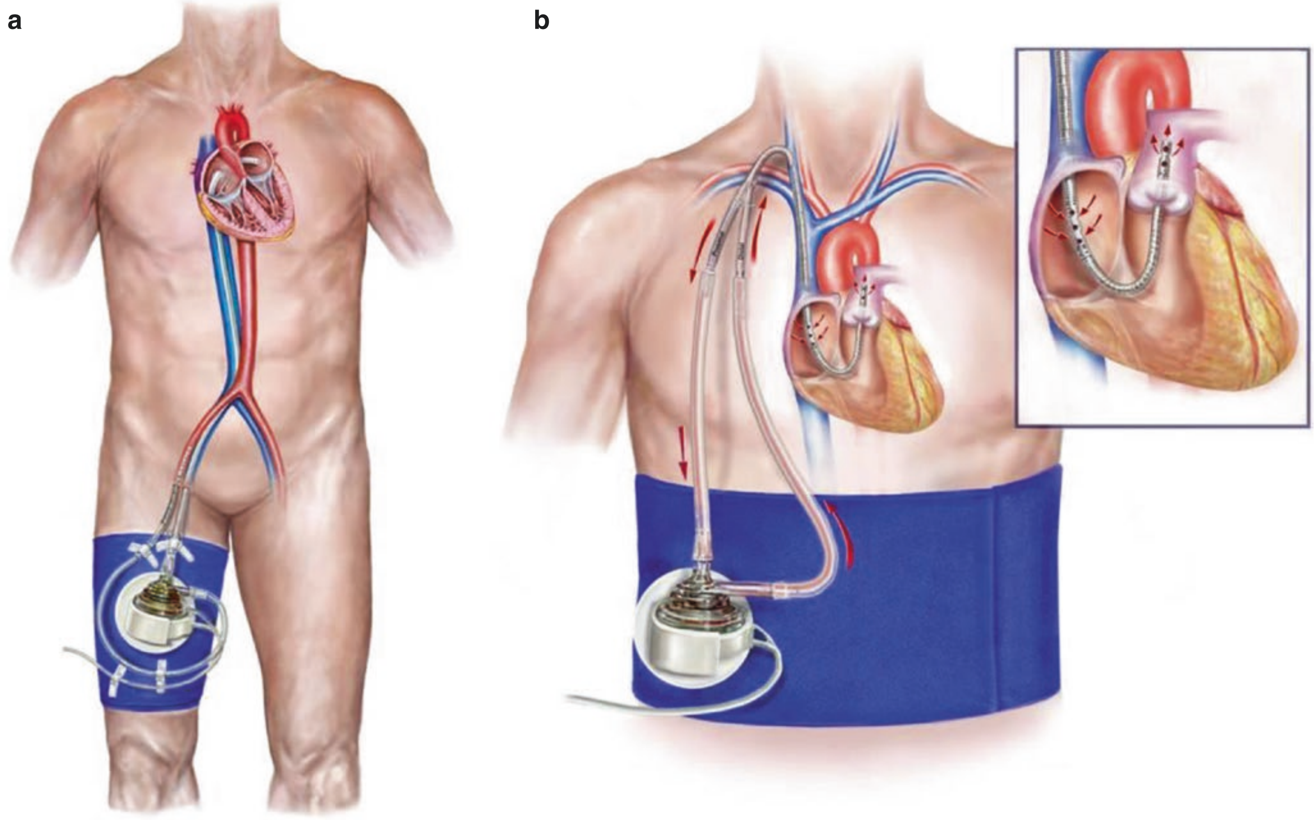


Fig. 69.2 TandemHeart percutaneous left and right ventricular support. (**a**) TandemHeart left atrium to femoral artery bypass circuit. (**b**) Tandem Protek Duo RVAD. *RVAD* right ventricular assist device. (Images provided by CardiacAssist, Inc. dba TandemLife, Pittsburgh, PA, USA)

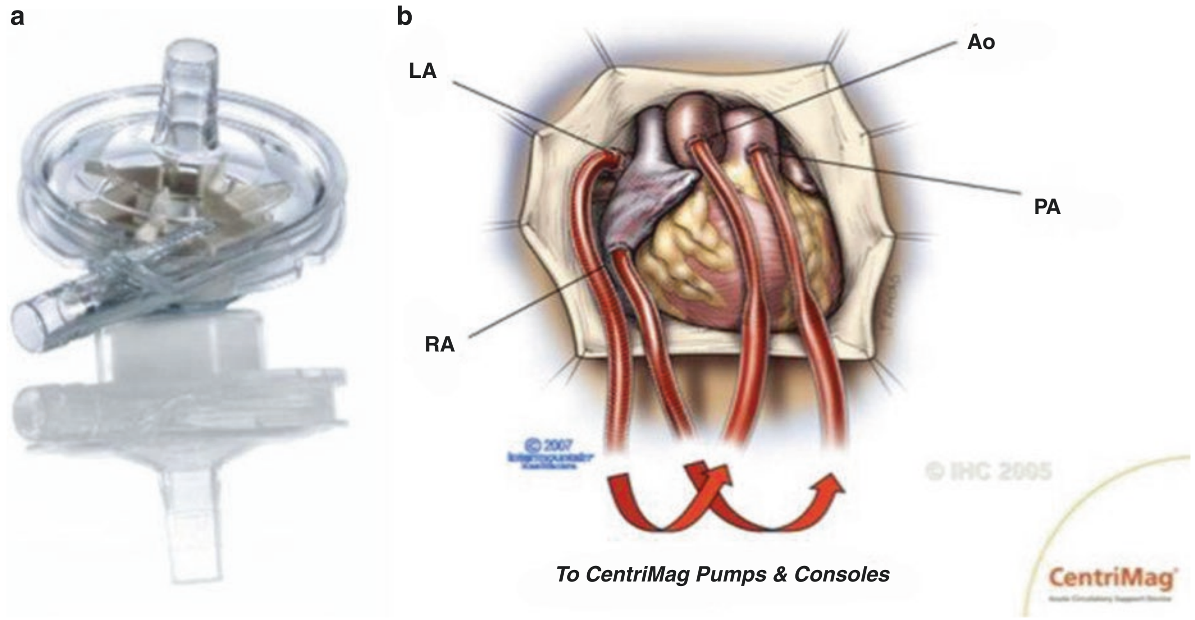
implant [23–25]. A subset of patients, though, has been successfully bridged to cardiac transplantation (average support 7.6 ± 3.2 days) [26]. One of the main concerns with the TandemHeart is the risk of the unsecured cannula slipping from the LA back into the RA, which would cause massive right-to-left shunt and systemic hypoxemia. This requires complete immobilization of the patient to minimize this risk.

Percutaneous RV support with the TandemHeart™ pump was first explored using bifemoral vein access with a 21 Fr inflow cannula positioned in the RA and a separate 21 Fr outflow cannula positioned in the main PA [27, 28]. The outflow cannula also can be placed via the right internal jugular (IJ) vein and positioned in the main PA [29]. Either configuration, though, requires the placement of two cannulas. The recent approval of the percutaneous, dual lumen Protek Duo cannula, has made it possible to provide RV support with just one venous access site while facilitating mobility and ambulation (Fig. 69.2a). When placed via the right IJ vein, the inflow cannula aspirates blood from the RA to the TandemHeart™ pump and the outflow is positioned in the main PA. The circuit is also compatible with an oxygenator, if needed, and delivers up to 5 L/min of flow. In a recent case series of 17 patients that underwent Protek Duo placement for RV support, 23% were successfully weaned and overall mortality rate was 41% [30].

CentriMag™

The CentriMag™ is an extracorporeal, centrifugal pump capable of delivering up to 10 L/min of flow, employing a magnetically levitated rotor without any bearings, seals, or shafts. These unique features enable wider gaps with minimal friction, hemolysis, or thrombus formation. It can be utilized for various clinical indications including, but not limited to, post-cardiotomy shock, primary graft dysfunction following cardiac transplantation, and as a temporizing, bridge to decision modality for acute refractory cardiogenic shock. For biventricular assistance (BiVAD), cannulation entails either conventional sternotomy or minimal access thoracotomy, with cannulation of the (1) RA and PA and (2) LV or LA and aorta for the right and left VAD configurations, respectively (Fig. 69.3). In some instances, only single ventricular support is needed, such as temporary RV support following implantable LVAD placement (Fig. 69.4).

In a 2014 meta-analysis of over 50 studies and nearly 1000 patients, the CentriMag™ pump was utilized as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CentriMag

Fig. 69.3 Centrimag BiVAD support. (**a**) The Centrimag pump (**b**) Centrimag biventricular assist device configuration with cannulation of the RA to PA (RVAD) and the LV or LA to the aorta (LVAD). *BiVAD* biventricular assist device, *RA* right atrium, *PA* pulmonary artery, *RVAD* right ventricular assist device, *LV* left ventricle, *LA* left atrium, *LVAD* left ventricular assist device

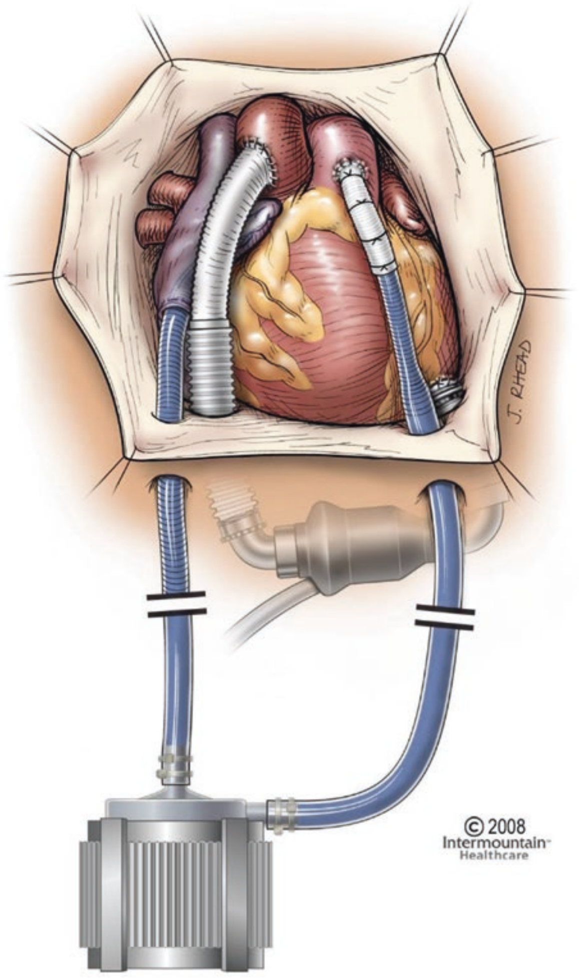

Fig. 69.4 Centrimag temporary RVAD support. *RVAD* right ventricular assist device

temporary VAD support or as a component of the ECMO circuit in 72% and 25% of the cases, respectively [31]. In 80 patients supported with CentriMag™ RVAD, Bhama and colleagues reported median support duration of 6 days with >80% successful weaning following heart transplant or durable LVAD, but <50% weaning rates for other forms of post-cardiotomy shock [32]. A comprehensive meta-analysis of short-term MCS (N = 4151 patients) included 128 patients supported with BiVAD CentriMags™. In this cohort, the mean duration of support was 20 days and survival to hospital discharge was 66% (range 58–74%) [33].

Post-operative Management and Weaning

In the early post-procedural period, it is critical to have continuous hemodynamic monitoring with a pulmonary artery catheter to follow filling pressures, mixed venous oxygen saturation, and systemic vascular resistance to minimize inotropic and/or vasopressor medications. Routine and frequent laboratory analyses are needed to ensure adequate anticoagulation and perfusion and to minimize hemolysis. Concomitant treatment of volume overload with diuretics or institution of continuous veno-venous hemodialysis (CVVH) in cases of oligo- or anuric renal injury is an important factor to optimize hemodynamics.

Although there is little published evidence surrounding device weaning, most experienced centers have developed an internal strategy. Once inotropic and vasopressor support has been minimized or eliminated, we perform transthoracic or transesophageal echocardiography with simultaneous hemodynamic assessment to determine minimally necessary pump settings. If all parameters remain stable with low-dose inotropic support during a step-wise pVAD wean, we proceed with explant. Once the decision to explant is made, however, it is vitally important to have a priori contingency plans in place for salvage or palliation in the event of failed explantation. Similarly, for patients unable to wean and who are not candidates for durable LVAD or cardiac transplant, a terminal wean with palliative support should be considered.

Conclusions

Cardiogenic shock continues to have a high mortality rate despite early interventions including revascularization, LV decompression, and an improvement in hemodynamics. An expert consensus statement advised that temporary MCS was superior to pharmacologic therapy and that early and appropriate use of MCS may be considered for patients having high risk PCI or with cardiogenic shock [34]. The data, however, are insufficient to recommend one particular form of mechanical support over another. The development of a "shock team" that is inclusive of interventional and heart failure cardiologists as well as a transplant/VAD cardiac surgeon is imperative to select the right device for the right patient at the right time and with the right exit strategy.

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Heart Transplantation

70

Aravinda Page and Yasir Abu-Omar

High Yield Facts

- More than 120,000 human heart transplants have been performed since the first heart transplant in 1967.
- Heart transplantation is the gold-standard therapy for patients with end-stage heart failure.
- Heart transplantation is limited by the availability of suitable donor hearts.
- In the modern era, heart transplantation allows a median survival of at least 11 years post-operatively.
- The highest risk of mortality is in the first year post-transplant with primary graft failure being the leading cause of this early mortality.
- Younger and older patients have the highest relative risk of mortality within 5 years of transplantation, with recipients transplanted around the age of 50 carrying the lowest risk.
- Globally, donation following brain stem death has been the major source of donor hearts but recently donation following circulatory determined death is being adopted as a source of suitable donor hearts.
- Developments in the fields of transportable machine perfusion and preservation/reconditioning of donor hearts are allowing for an increasing number of potential donor hearts to translate into clinical transplants.

Introduction

The incidence of heart failure has gradually increased with earlier recognition of this debilitating disease. Furthermore, with the development of heart failure services more patients are being referred to transplant teams for consideration of heart transplantation and mechanical circulatory support.

Since the first heart transplant in 1967[1], more than 120,000 heart transplants have been performed and recorded in the International Society of Heart and Lung Transplant (ISHLT) registry [2]. The results of heart transplantation have continued to improve due to better pre-operative selection and early donor management as well as post-operative management and immunotherapy. Heart transplantation has also been shown to offer a significant survival advantage over medical therapies in patients with AHA class D heart failure [3].

The biggest challenge facing heart transplantation is the shortage of suitable donors. When heart transplantation was first performed, criteria for brain stem death had not been established and all donations were from donors after circulatory determined death or non-heart beating donors. Since the introduction of clinical criteria for the diagnosis of brain stem death in the 1970s [4], the main stay of heart transplantation has been from donors following brain stem death (heart-beating donors). However, a few institutions have re-established heat transplant programmes from donors following circulatory determined death (non-heart beating donors) in a bid to expand the donor pool [5–7].

The majority of heart transplants are performed as a single organ transplant, however there are a number of combined heart-lung transplants performed in patients with irreversible pulmonary hypertension as well as combined heart-kidney and heart-liver transplants for those with multiple irreversible organ dysfunction.

Indications and Patient Selection

Recipient Criteria

Patients referred with heart failure secondary to non-ischaemic cardiomyopathy make up more than 55% of heart transplant recipients. The diagnosis of coronary artery

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disease makes up 35% of recipients with the remainder being made up of valvular heart disease, congenital heart disease and re-transplants [2].

Heart transplantation should be considered in patients with heart failure that is irreversible and refractory to medical or surgical treatment. These patients display New York Heart Association (NYHA) class III–IV symptoms despite optimal heart failure therapy and may have undergone cardiac resynchronization therapy (CRT) and be fitted with an implantable cardioverter defibrillator (ICD) as indicated. Patients who are considered for heart transplantation assessment have evidence of a poor prognosis as indicated by composite scoring systems such as the Heart Failure Survival Score or Seattle Heart Failure Model [8].

Cardio-pulmonary exercise testing also plays a vital role in transplant assessment and a VO_2 max <12 ml/kg/min if on beta-blockade, or <14 ml/kg/min if not on beta-blockade, while ensuring respiratory quotient <1.05 predicts a poor prognosis without intervention and therefore should be considered as an indication for transplantation [9]. Similarly markedly elevated levels of B-type natriuretic peptide (BNP) also predict a poor prognosis without intervention. Elevated pulmonary vascular resistance (PVR) as estimated by using a right heart catheter is important in assessing suitability for transplantation. A fixed PVR >6 WU is considered a contraindication for heart transplantation alone [10].

Heart transplantation should also be considered in the more acute setting of patients who present in cardiogenic shock requiring continuous support with intra-aortic balloon counterpulsation or mechanical circulatory support in the form of ventricular assist devices. Additionally patients with intractable life threatening arrhythmias unresponsive to pharmacological or interventional treatments should also be considered for heart transplantation.

Risk factors and contraindications (relative and absolute) to heart transplantation are listed below.

- Intrinsic organ damage
- Sepsis (active bacterial or viral infection)
- Symptomatic peripheral or cerebrovascular disease
- Diabetes mellitus with microvascular complications (neuropathy, retinopathy, nephropathy)
- Current or recent neoplasm
- Severe lung disease
- Renal dysfunction (eGFR <40 ml/min/1.73 m^2)
- Recent pulmonary thromboembolism
- Pulmonary hypertension
- Weight: obesity or cardiac cachexia
- Psychosocial factors (substance abuse including tobacco, alcohol etc.)

Donor Criteria

Heart transplantation is limited by the severe shortage of suitable donor organs. This short supply has led to strategies such as early donor management to improve donor heart quality. The process of brain stem death results in catecholamine surge that can result in gross haemodynamic instability. Brain death has been shown to be associated with myocardial injury in up to 20% of donors after brain death (DBD) and myocardial dysfunction is seen in at least 40% [11, 12]. Further to this, the vasoplegic state following herniation of the brain stem may prompt the liberal use of vasopressors such as norepinephrine in the critical care setting. Unfortunately, high doses of these drugs have been shown to be associated with increased rates of primary graft dysfunction, particularly the right ventricle and higher post-transplant mortality in both the short and long-term [13, 14]. This is where donor management is critical to ensure optimization of filling pressures to optimize donor heart function and increase the probability of acceptance for transplantation.

Echocardiography plays a vital role not only in assessing cardiac function but also in ensuring the absence of valvular and congenital abnormalities that might preclude acceptance for transplantation. Myocardial dysfunction seen following brain death is often reversible and has been shown to improve following brain stem death [15, 16]. Valvular abnormalities usually preclude the use of the heart for transplantation but the use of young donor hearts with bicuspid aortic valve disease after surgical correction has been reported [17].

Suggested criteria for an ideal DBD heart are listed below:

- Mean arterial pressure >60 mmHg
- Central venous pressure <12 mmHg
- Pulmonary capillary wedge pressure <12 mmHg
- Systemic vascular resistance 800–1200 dyne/s/cm^5
- Cardiac index >2.4 l/min/m^2
- Dopamine infusion <5 μg/kg/min
- Noradrenaline infusion <0.07 μg/kg/min

Evidence of coronary artery disease is assessed by coronary angiography where available, particularly in patients aged >45 years or alternatively is assessed by inspection and palpation for plaque at the time of organ retrieval. In the UK, coronary angiography is not routinely performed and assessment is based on visual inspection alone.

Organ Allocation

Organ allocation systems vary globally, but the underlying principles are to allocate organs according to the urgency status of the patient. The most urgent patients are generally those who are dependent on inotropic support together with temporary mechanical circulatory support. In situations where there is a significant distance between donor and recipient hospital, attention is also paid to the estimated allograft ischemic time due to varying transport times when allocating organs.

Donor organs are matched to suitable recipients based on ABO blood group [18]. In patients who are at risk of allosensitization to specific human leucocyte antigens (HLA) such as following blood transfusions, testing for anti-HLA antibodies is carried out. This is particularly relevant in patients with mechanical circulatory support who comprise more than a third of heart transplants being performed annually as they are likely to have had blood transfusions at some point [19]. Antibodies against incompatible donor ABO matching or HLA antigens can result in hyperacute rejection or antibody mediated rejection.

Procedure and Technical Considerations

Organ Retrieval

In the DBD setting, once the decision to proceed to retrieval is made, cardiectomy is performed after the donor is fully heparinised. The inflow is occluded at the level of the superior vena cava (SVC) and inferior vena cava (IVC) and the right heart vented by dividing the IVC at the level of the diaphragm. The left heart is vented via the left atrial appendage or by the division of the pulmonary veins (if the lungs are not to be used for transplantation). Cardioplegic arrest is achieved after cross-clamping of the aorta. Thereafter, the heart is dissected out ensuring to leave an adequate left atrial cuff for the purposes of lung retrieval where indicated. The heart is then placed in cold saline and in an insulated organ transport box for static cold storage or an ex-situ organ perfusion device.

In the donor after circulatory death (DCD) setting, the aim is to re-establish perfusion to the heart as quickly as possible following systemic heparinisation. This can be achieved by establishing a limited cardio-pulmonary bypass circuit following heparinisation following the exclusion of cerebral perfusion and then the heart is retrieved in a similar way as described [20, 21]. Alternatively, the heart is rapidly retrieved and placed immediately on an ex-situ organ perfusion device.

Organ Implantation

Heart transplantation is most commonly practiced using a bi-caval technique in the orthotopic position. First, the donor left atrium is anastomosed to the recipient atrial cuff forming the confluence of the pulmonary veins. This is followed by anastomoses of the pulmonary artery and aorta. Completion of the caval anastomoses may be performed once the cross-clamp in the donor is released to decrease the period of ischemia. Some centres also utilise a bi-atrial technique of heart implantation but this has been largely superseded by the bi-caval technique.

Haemodynamic and Clinical Outcomes

The most recent international data collated by the International Society of Heart and Lung Transplantation (ISHLT) from over 400 heart transplant centres and including over 40,000 patients has shown that heart transplantation carried out between 1992 and 2001 offers a median survival of 11 years. This is further extended to 13 years in patients who survive the first year after their heart transplant [2]. The greatest mortality risk following transplant is in the first year. In the immediate postoperative setting primary graft failure is the leading cause of mortality followed by non-cytomegalovirus (CMV) infections and multi-organ failure and can be attributed to more than two-thirds of all death post-transplant in the first year.

Infections are most common in the first year following transplantation and are mostly related to the higher use of immunosuppressive agents during that period.

Post-transplant survival is highly dependent on a number of donor factors; increasing donor age has been shown to correlate to poor post-transplant survival, particularly in the early post-operative period. Donor assessment is crucial with hypertension being identified as a risk factor, as is left ventricular hypertrophy >13 mm [22, 23].

Recipient factors such as age at transplant and aetiology of heart failure also influence post-transplant outcome. Transplantation for ischaemic cardiomyopathy carries a slightly greater risk than that for non-ischaemic cardiomyopathy. Congenital cardiomyopathy transplant recipients carry a much higher risk in the first year post-transplant but much better 10-year survival. Re-transplants carry a higher risk of mortality than primary transplants, and this is notably higher particularly in the first year post-transplant [24]. Younger and older patients have the highest relative risk of mortality within 5 years of transplantation, with recipients transplanted around the age of 50 carrying the lowest risk [22]. Other risk factors include diabetes and other organ failure. With more experience in pre-transplant mechanical circulatory support, recent data suggests that the use of mechanical circulatory support (MCS) does not correlate with worse survival outcomes except in the setting of pre-transplant extra-corporeal membrane oxygenation use and the presence of biventricular support or total artificial heart devices [25].

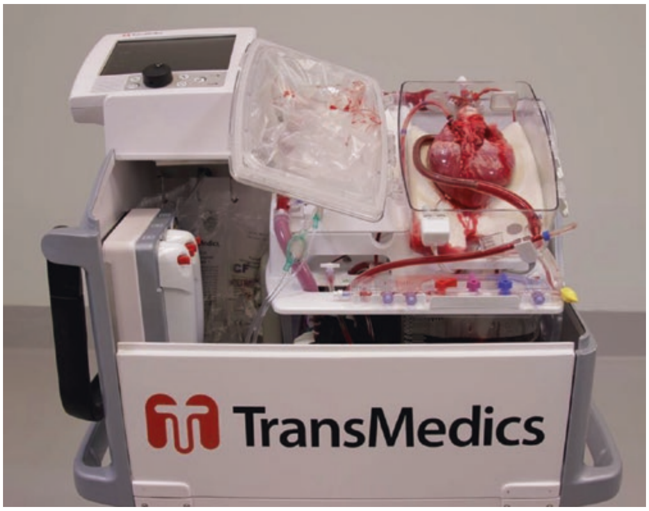

Fig. 70.1 Organ Care System (OCS™ HEART) which allows for normothermic perfusion of donor hearts during transport. (Courtesy of Transmedics, Inc.)

Allograft ischaemic times less than 4 hours have been shown to be associated with significantly better outcomes and any extension beyond this when cold storage is used for organ preservation markedly increases the risk [25]. However, the use of ex-situ perfusion platforms in clinical use will allow for longer transport times without elongating the allograft ischaemic time (Fig. 70.1). To date, such a platform has been shown to be non-inferior to standard cold storage preservation [26].

Complications

Primary Graft Dysfunction

There has been significant variation in the true incidence of primary graft dysfunction (PGD), as until now the definition has varied. ISHLT recently proposed a consensus document defining PGD as the onset of left, right or biventricular dysfunction within the first 24 h of transplantation for which there is no secondary cause and graded as mild, moderate or severe. Severe PGD has always been associated with the use of MCS and carries a mortality of up to 40%.

Acute Rejection

Before the turn of the century, acute rejection was a major cause of hospitalisation for patients following transplant. With advances in immunosuppression, the incidence of rejection has continued to decrease, as has the mortality associated with it. The risk of rejection is highest in the first year post-transplantation and therefore immunosuppression is at its maximum then, and is tapered down thereafter. Induction immunotherapy with rabbit anti-thymocyte globulin (rATG) has been shown to decrease the incidence of early rejection. Most maintenance immunosuppression regimes consist of a steroid, a calcineurin inhibitor and mycophenolate mofetil. Routine surveillance biopsies allow for the early detection of rejection, however rejection should always be suspected in the event of depressed ventricular function, often associated with other clinical manifestations such as pyrexia.

Cardiac Allograft Vasculopathy

Cardiac allograft vasculopathy (CAV) is seen in more than half of the patients 10 years post-transplant and is a significant risk factor for post-transplant mortality [22]. On angiography CAV is characterised by diffuse disease of the coronary arteries.

Malignancy

Long-term use of immunosuppressive agents is thought to be associated with a higher risk of malignancy, particularly skin cancers. Post-transplant lymphoproliferative disorder is a proliferation of B-cells and is thought to be related to infection with Epstein-Barr virus [27].

The Future

Heart transplantation continues to grow in demand with progressively improving results but is limited by the availability of suitable organs. At present donor hearts are transported largely in cold storage, but with the development of ex-situ perfusion methods, not only are we able to shorten ischaemic times to improve the prognosis post-transplant, but also allow for longer travel time without the restriction of allograft ischaemic time. Additionally the use of ex-situ perfusion has allowed for the use of extended criteria donors and the establishment of successful DCD heart transplant programmes [7, 28]. This has allowed for increasing transplant activity and donor organ utilization. Furthermore, this platform allows for the unique opportunity to recondition organs. Methods of supporting organs ex-situ continue to develop to be able to sustain the viability of organs ex-situ longer, provide the opportunity for pharmacological post-conditioning as well as the application of novel targeted therapies to optimise and improve the organ pre-transplantation.

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Heart-Lung Transplantation

71

Don Hayes Jr., Michael S. Mulvihill, and David McGiffin

High Yield Facts

- The number of combined heart-lung transplants worldwide has declined substantially with less than 50 performed in 2015.
- The accepted indications for heart-lung transplantation are Eisenmenger syndrome with an uncorrected intracardiac defect, uncorrectable congenital heart disease with atresia or diffuse severe hypoplasia of the pulmonary arteries, and coexistent severe cardiopulmonary disease with advanced heart or lung failure.
- The immunosuppressive protocol for heart-lung transplantation more closely follows that used in lung rather than heart transplantation.
- Allograft rejection of the heart and lungs after heart-lung transplantation is asynchronous.

Introduction

Combined heart-lung transplantation (HLTx) was a natural extension of cardiac transplantation and at one time was the preferred transplant procedure for some patients with end-stage lung disease such as cystic fibrosis, with the recipient heart being used for a domino-donor transplant. However, the number of combined heart-lung transplants worldwide has declined substantially. Although not necessarily reflecting the world's complete HLTx activity, the International Society of Heart and Lung Transplantation (ISHLT) Registry recorded just less than 300 heart-lung transplants in 1989, compared to 2015, when the number of heart-lung transplants were just less than 50 [1]. The reason for this decline is in part the realization that patients with end-stage lung disease, even with an extremely adversely remodeled right ventricle can undergo lung transplantation with results equivalent to HLTx [2, 3]. Also, in some countries, the wait time for a heart-lung bloc may be considerably longer than for single-donor heart or lungs.

History

Highlights of the experimental and clinical development of HLTx are as follows:

- Transplantation of a heart-lung bloc into the neck of a recipient animal by Carrell in 1907 [4].
- Performance of orthotopic HLTx in experimental model without the use of cardiopulmonary bypass by Demikhov in the 1940s and 1950s [5].
- A number of other investigators including Webb (1950s) [6], Longmore (1960s) [7], and Lower (1970s) [8], carried out a variety of experimental investigations into HLTx, and all reported post-transplant impaired respiratory mechanics.
- The loss of the Hering-Breuer inflation reflex following HLTx in non-primate animals resulting in impaired respiratory mechanics was thought to represent a fundamental impediment to successful HLTx until it was demonstrated that the Hering-Breuer reflex was not essential for normal respiratory mechanics in primates [9].
- First clinical HLTx by Cooley in 1968 involving an infant with complete atrio-ventricular septal defect and pulmonary hypertension with early death [10].
- HLTx performed by Lillehei in 1969 with early death [11].

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- HLTx performed by Barnard in 1971 found that the patient had normal respiratory mechanics but died of airway necrosis (bilateral bronchial rather than tracheal anastomosis) [12].
- First successful HLTx by Reitz occurred in 1981 [13]. Success was in part due to a convergence of extensive experimental work and cyclosporine-based immunosuppression.

Indications for Heart-Lung Transplantation

The accepted indications for HLTx [14] are:

- Eisenmenger syndrome with an uncorrected intracardiac defect
- Uncorrectable congenital heart disease with atresia or diffuse severe hypoplasia of the pulmonary arteries
- Coexistent severe cardiopulmonary disease with advanced heart or lung failure

Pulmonary hypertension is no longer an indication for HLTx in adults since reverse remodeling of a severely adversely remodeled right ventricle can be expected after lung transplantation.

Eisenmenger Syndrome

Patients with post-tricuspid shunts (the majority of the patient population) develop plexogenic pulmonary arteriopathy with severe pulmonary hypertension, uncorrectable hypoxemia, and marked erythrocytosis as a result of a hemodynamically non-restrictive communication at the ventricular or aortic/pulmonary artery level so that the Eisenmenger reaction begins in infancy. The timing of HLTx in these patients can be a vexing problem as their survival is considerably better than that of patients with pulmonary arterial hypertension (Fig. 71.1) and arguably at an early time course of the process better than that of the survival after HLTx [15–22]. The timing of listing for HLTx is based on worsening cyanosis and progressive symptoms of fatigue and breathlessness. In these patients, an alternative to HLTx is lung transplantation with correction of the intracardiac defect, but superiority of one technique over the other has not been convincingly demonstrated.

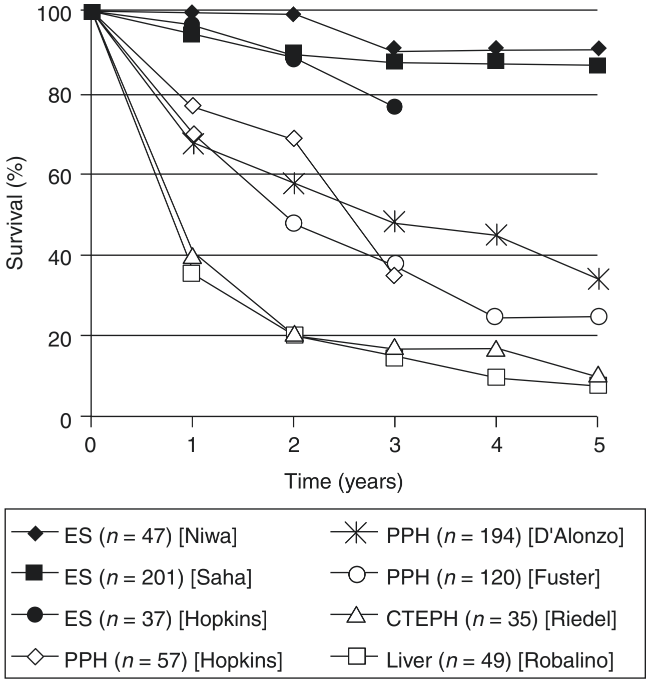

Fig. 71.1 Survival of patients with severe pulmonary hypertension derived from multiple studies. The number of patients in each study is within parentheses and the reference number for each study is in brackets. *ES* Eisenmenger syndrome, *PPH* primary pulmonary hypertension, *CTEPH* chronic thromboembolic pulmonary hypertension, *liver* portopulmonary hypertension. (Modified from Hopkins et al. [15] with permission; Niwa et al. [16], Saha et al. [17], Hopkins et al. [18], D'Alonzo et al. [19], Fuster et al. [20], Riedel et al. [21], and Robalino et al. [22])

Uncorrectable Congenital Heart Disease with Atresia or Hypoplasia of the Pulmonary Arteries

HLTx is the procedure of choice in patients with uncorrectable congenital heart disease and poor ventricular function where, because of atresia or diffuse hypoplasia of the pulmonary arteries, it is not possible to make a connection between a donor pulmonary artery and the native pulmonary circulation. Many of these patients though have had one or more shunt procedures and may have very extensive aortopulmonary collaterals and as a consequence HLTx may incur a substantial operative risk from bleeding.

Combined Cardiac and Pulmonary Disease

This is an unusual indication for HLTx but could be considered in patients with end-stage heart disease and concomitant lung disease that is too severe for heart transplantation alone and vice versa [14]. The most common situation where this could occur would be patients with smoking-related emphysema and coronary artery disease. Currently, there is no information to confidently guide decision-making, but it would be prudent to recommend HLTx over lung transplantation alone for patients with severe lung disease and obstructive coronary disease that is not manageable by percutaneous coronary intervention with more than mild left ventricular dysfunction.

Selection Criteria for Heart-Lung Transplantation

A consensus on the selection of recipients for lung transplantation is published by the ISHLT [23], which applies to the selection process for HLTx with certain caveats.

Recipient Age

When considering a potential recipient's age, the usual issues of chronological age versus biological age are considered. While the chronological age of heart or lung transplant recipients has been creeping upwards (up to 70 years for hearts and >70 years for prudently chosen lung recipients), the chronological age for heart-lung recipients is pegged in most programs no greater than 65 years of age. This, in part, reflects the inexorable depletion of physical reserves and subsystem organ reserves in patients who require HLTx for uncorrectable congenital heart disease with decades of hypoxemia, erythrocytosis, and systemic venous hypertension. A very careful assessment of physical reserves, frailty, and nutritional status are particularly important considerations for prudent recipient selection.

Aortopulmonary Collaterals

Patients with complex congenital heart disease with atresia or hypoplasia of the central pulmonary arteries may have very extensive aortopulmonary collaterals, which can potentially create a situation of unmanageable and unsurvivable intraoperative bleeding. Therefore, in the evaluation of these patients, defining the extensiveness of aortopulmonary collaterals in particular and making the calculation about the degree of difficulty of the transplant procedure is mandatory.

Previous Thoracic Surgery

Previous median sternotomy (or more than one) or thoracotomies, particularly for shunt procedures may increase the operative risk of HLTx because of bleeding. However, not all previous operations would increase the risk to the same degree. For example, a sternotomy for an atrial septal defect has a considerably lower risk than multiple shunts through thoracotomies, particularly if there are aortopulmonary collaterals present. These relative contraindications must be included in the calculation of the operative risk together with other important considerations such as surgeon experience with these potentially very difficult cases and patient physical reserves to withstand the consequences of very destabilizing bleeding.

Technique of Heart-Lung Transplantation

The technique of HLTx embodies many principles of the techniques for heart and lung transplantation.

Minimization of injury to the heart and lungs during the ischemic time is critical to the outcome and is achieved with preservation solutions and perhaps the most important ingredient is hypothermia to reduce metabolic demands. Although the data is not compelling, there is a tendency to use intracellular solutions (higher potassium and lower sodium and calcium) for myocardial preservation (University of Wisconsin solution, St Thomas's solution for example) and extracellular solutions (higher concentrations of sodium and lower concentrations of potassium) for lung preservation (such as Perfadex).

The Donor Procedure

The principles of the procurement of the heart-lung bloc are as follows:

- Following heparinization, the superior vena cava is ligated or clamped.
- Opening of the inferior vena cava to allow exsanguination followed by cross clamping of the ascending aorta.
- The pulmonary flush solution and cardioplegic solutions are commenced and the left atrial appendage is amputated to allow pulmonary flush solution to escape from the left atrium.
- One of the important considerations is to ensure absolute hemostasis of the heart/lung bloc particularly on the posterior aspect as it may be difficult in the recipient to gain hemostasis following implantation.
- Throughout the flush, the lungs are gently ventilated with 100% oxygen.
- Following the completion of the flush, the inferior vena caval incision is completed, superior vena cava transected, ascending aorta transected, and pericardium anterior to pulmonary veins excised with electrocautery.
- The inferior pulmonary ligaments are divided and with electrocautery the pleural reflections posterior to the hilum of each lung are divided and bronchial vessels are sought and secured with Hemoclips.

- The lungs are inflated, the trachea clamped between two straight Kocker clamps and divided between the clamps. The heart-lung bloc is dissected from the esophagus and remaining pleural attachments with electrocautery, the trachea stapled and triple bagged with Perfadex in the inner bag and ice slush in the two outer bags for transportation.

The Recipient Procedure

The principles of the recipient procedure are as follows:

- Although a median sternotomy has been the usual approach a bilateral anterolateral trans-sternal thoracotomy (clamshell incision) has distinct advantages as it allows better access to bleeding from the posterior mediastinal tissue of the recipient and the heart-lung bloc.
- After establishing cardiopulmonary bypass by cannulation of the ascending aorta and bicaval cannulation, the recipient heart is excised by transecting the ascending aorta, main pulmonary artery, left atrium, and superior and inferior vena cava. In patients with extensive aortopulmonary collaterals, the process of excision of the recipient heart and lungs must be performed very slowly and each collateral dealt with individually to avoid massive and uncontrollable bleeding (Fig. 71.2).
- The pleural cavities are opened and the left and right bronchi are stapled (Fig. 71.3) and divided, and the pulmonary veins and pulmonary artery on each side divided and the lungs removed after dividing the pleural attachments.

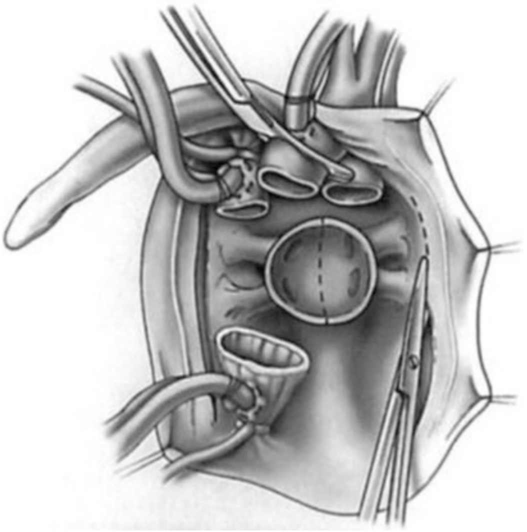

Fig. 71.2 The recipient heart is excised by a standard cardiectomy. The traditional operation involves fashioning phrenic nerve pedicles but this may not be necessary. (From Kirklin et al. [14] with permission)

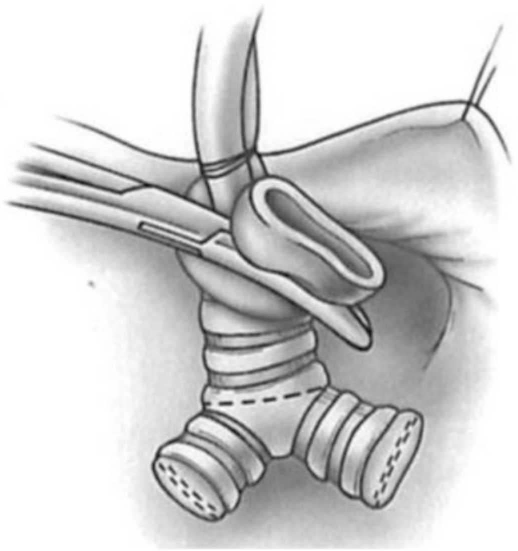

Fig. 71.3 The recipient lungs are removed by stapling each bronchial stump. The stapled bronchi and carina must then be mobilised and the trachea transected (indicated by dashed line). It is important that tracheal dissection does not occur any higher than the transection line to preserve tracheal blood supply. (From Kirklin et al. [14] with permission)

- It is not necessary to excise all of the remaining main pulmonary artery, left atrium, and pulmonary veins particularly if there are extensive aortopulmonary collaterals. Furthermore, minimizing excision of residual pulmonary artery will prevent injury to the left recurrent laryngeal nerve.
- It is critical that meticulous hemostasis is achieved before the heart-lung bloc is placed into the chest.
- The traditional technique involved mobilizing each phrenic nerve on pedicles with a fenestration in the pericardium posterior to the phrenic nerves through which the hila of the lungs would pass. However, this is unnecessary and the lungs can be placed anterior to the phrenic nerves without causing any traction injury and furthermore allows easier rotation of the heart-lung bloc to deal with any posterior bleeding [24].
- The tracheal anastomosis (Fig. 71.4) is performed with a polypropylene suture depending on programmatic preference, and the anastomosis may be wrapped with a pedicled pericardial flap.
- The inferior and superior vena caval anastomoses are performed followed by the aortic anastomosis (Fig. 71.5).
- The heart-lung bloc is then reperfused and when cardiac function is robust cardiopulmonary bypass is discontinued.

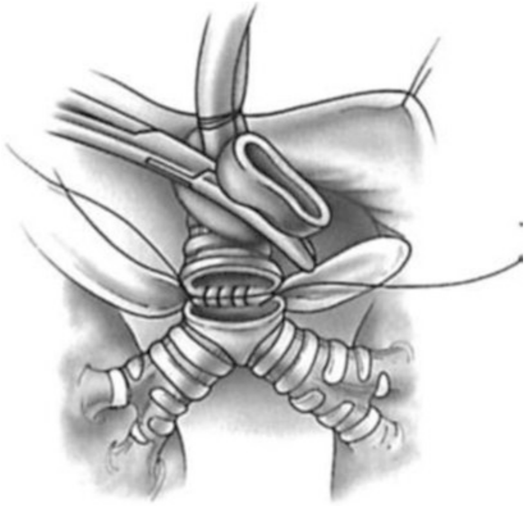

Fig. 71.4 The heart-lung bloc is placed in the pericardial cavity and the tracheal suture line is performed with a continuous polypropylene suture. A pedicle pericardial flap which can be incorporated into the tracheal suture line as indicated (From Kirklin et al. [14] with permission)

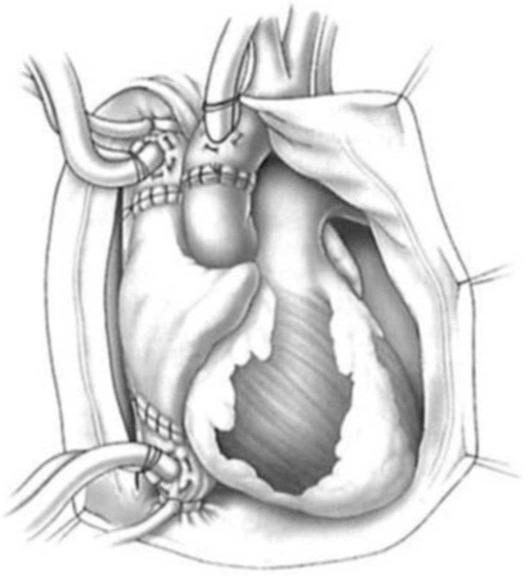

Fig. 71.5 The inferior vena caval, superior vena caval and aortic anastomoses are then performed. (From Kirklin et al. [14] with permission)

Postoperative Management

The postoperative management of these patients embodies the same principles of management of patients after heart and lung transplantation. One particular postoperative concern after HLTx in patients with extensive aortopulmonary collaterals is postoperative bleeding which may still occur despite meticulous hemostasis during the operation. Return to the operating room for evacuation of accumulated thrombus may be required and pulmonary primary graft dysfunction may be precipitated by the infusion of large volumes of blood products in these patients.

Immunosuppression

The principles of immunosuppression in patients after HLTx is the same as those after heart and lung transplantation. There is a lot of variability among transplant programs as far as the details of immunosuppressive protocols are concerned but they embody the following principles:

- An initial *induction* immunosuppression to reduce the probability of early rejection and promote graft acceptance.
- *Maintenance* therapy for chronic immunosuppression.
- *Augmented* immunosuppression at the time of acute rejection.

A variety of immunosuppressive protocols exists for both heart and lung transplantation; but after HLTx, immunosuppression in general more closely follows that used in lung rather than heart transplantation.

Induction therapy usually involves either cytolytic therapy or an interleukin 2 (IL-2) receptor blockade. *Maintenance* immunosuppression is based on triple drug therapy with a calcineurin inhibitor, a cell cycle inhibitor and corticosteroids. A proliferation signal inhibitor such as everolimus or sirolimus may be used in conjunction with or replacement for either a calcineurin inhibitor or a cell cycle inhibitor usually because of renal dysfunction, the onset of chronic lung allograft dysfunction or malignancy.

Complications

Acute Rejection

Acute rejection after HLTx follows the same immunological and histopathological processes as in heart and lung transplantation separately, although there are specific nuances in HLTx.

- It was once assumed that rejection of the heart and lungs after HLTx was synchronous and that when cardiac rejection was diagnosed by endomyocardial biopsy then rejection of the lung could be assumed. It is now known that rejection of the heart and lungs in HLTx is asynchronous.

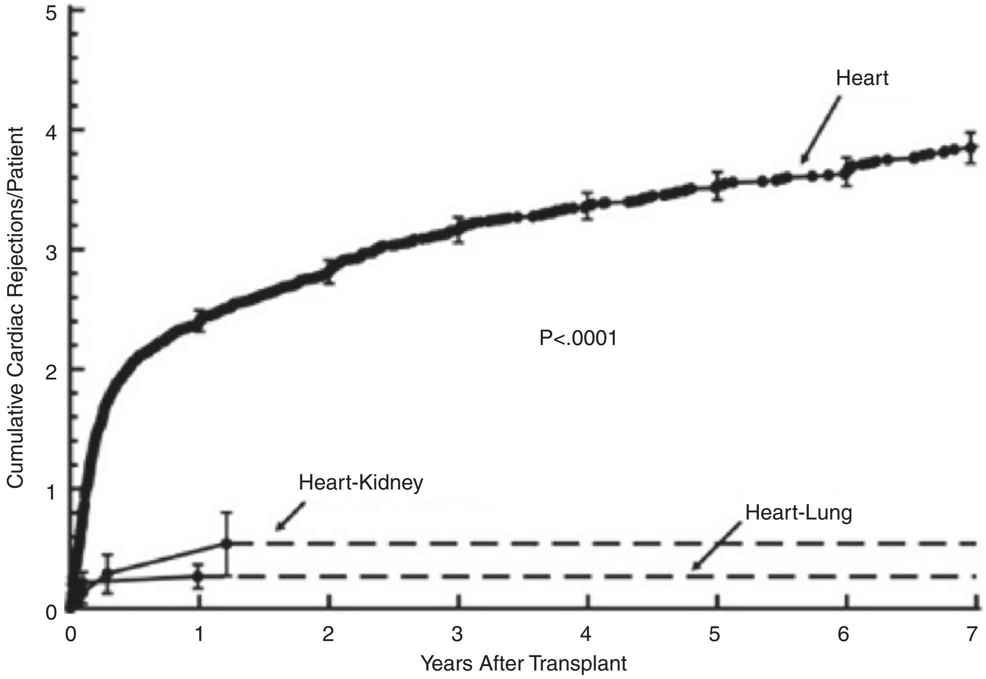

Fig. 71.6 Cumulative incidence of acute cardiac rejection after heart, heart-lung and heart/kidney multi-organ transplantation. (*Reprinted from* Pinderski et al. [25] with *permission from Elsevier*)

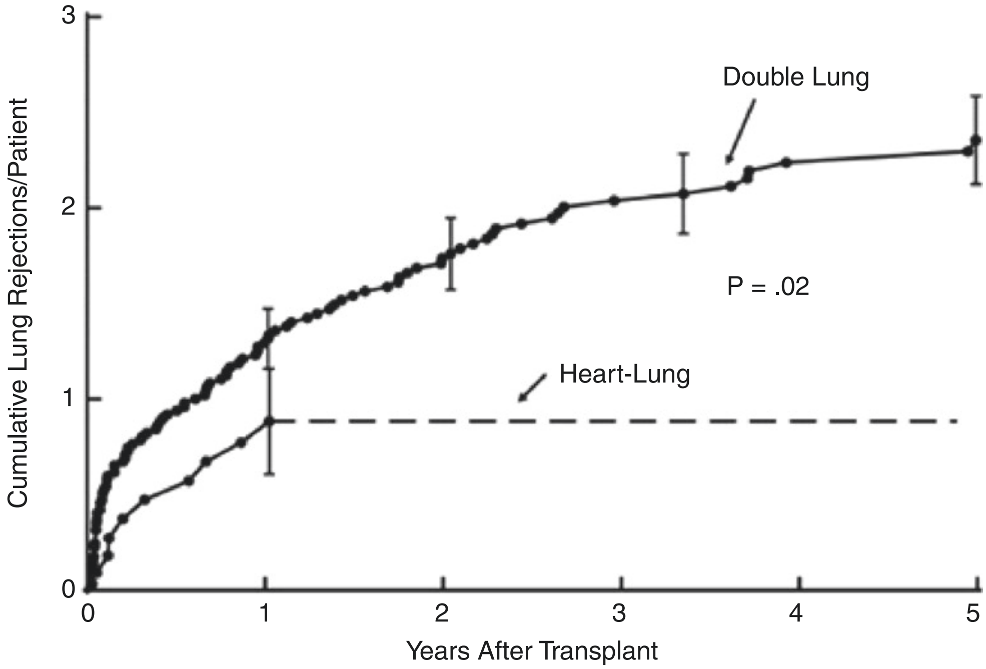

Fig. 71.7 Cumulative incidence of acute lung rejection after double lung or heart-lung transplantation. (*Reprinted from* Pinderski et al. [25] with *permission from Elsevier*)

- After HLTx, there appears to be a protective effect of multiple organ transplantation from acute rejection. In a study by Pinderski et al. [25], the probability of acute cardiac rejection within the first 3 months after HLTx was significantly less than that occurring in heart recipients (Fig. 71.6).
- The same protective effect is seen with respect to lung rejection in heart-lung recipients where the probability of lung rejection is considerable less than in patients undergoing double lung transplantation (Fig. 71.7).
- The incidence of acute cardiac rejection after HLTx is so low that many programs do not routinely perform endomyocardial biopsy.
- *Augmented* immunosuppression for the treatment of acute rejection involves bolus corticosteroids and in higher grades of rejection or recalcitrant rejection, cytolytic therapy.

Airway Complications

Specific nuances exist for airway complications after HLTx as compared to lung transplantation.

- The fundamental etiology of airway complications after lung transplantation (bronchial anastomosis) and HLTx (tracheal anastomosis) is airway ischemia, which has a spectrum of injury from mucosal damage through to airway necrosis.
- The incidence of airway injury after single or bilateral lung transplantation is between 4% and 14% [26–28], but the risk of tracheal injury after heart and lung transplantation is approximately half that of bronchial anastomoses after lung transplantation [29–30].
- One of the reasons for this is the presence of coronary-tracheal collateral vessels, which are usually small and non-functional but may become functional and provides significant systemic blood supply to the carina after HLTx. Further evidence of the importance of coronary-tracheal collaterals is the substantial incidence of airway complications after en bloc double lung transplantation where the coronary-tracheal collaterals have been divided since the heart was not transplanted with the lungs.

Chronic Lung Allograft Dysfunction

The bronchiolitis obliterans syndrome (BOS) phenotype of chronic lung allograft dysfunction (CLAD) is a major cause of mortality after HLTx.

- The study by Pinderski et al. [25] demonstrated that the freedom from BOS after HLTx is similar to that after double lung transplantation (Fig. 71.8). While acute lung rejection is a risk factor for BOS, non-immunological factors play a very important role in its etiology and may explain the lack of protective effect from multi-organ transplantation for chronic rejection of the lung.

Cardiac Allograft Vasculopathy

Data supports the inference that HLTx does have a protective effect on the development of cardiac allograft vasculopathy (Fig. 71.9) and probably reflects the important consequence of the lower incidence of acute cardiac rejection after HLTx compared to heart transplantation alone.

Graft-Versus-Host Disease

A very rare but potentially lethal complication of HLTx is graft-versus-host disease (GVHD) as a result of the significant amount of lymphoid tissue that is transplanted with the heart-lung bloc. Acute GVHD presents in a similar fashion to that after bone marrow transplantation with fever, colitis, pulmonary infiltrates and a maculopapular rash. GVHD is diagnosed by an immediate skin biopsy and HLA typing of the peripheral lymphocytes.

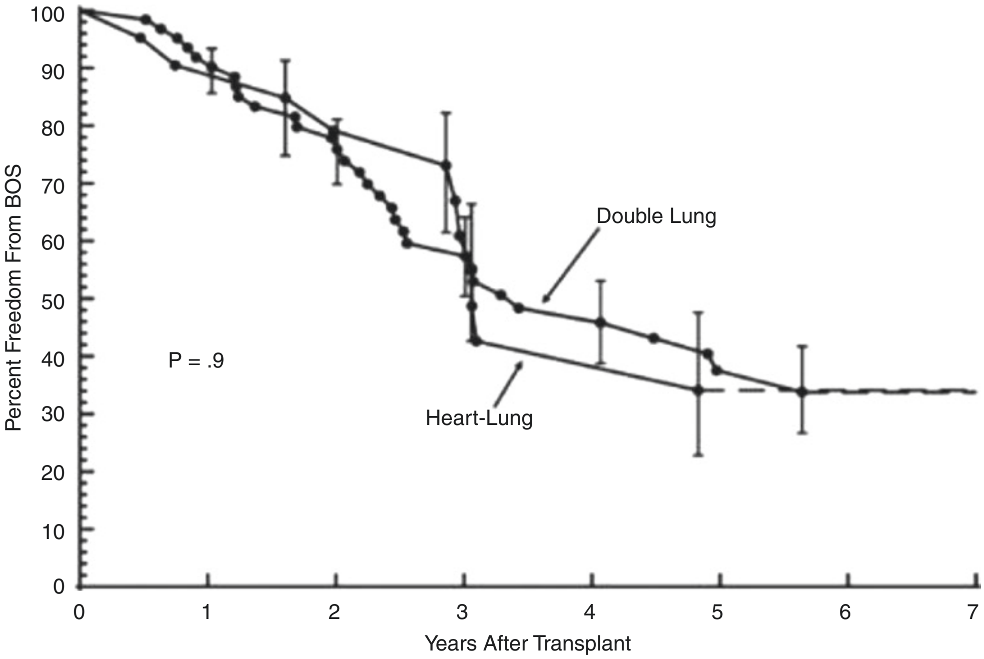

Fig. 71.8 Kaplan-Meier depiction of freedom from bronchiolitis obliterans syndrome after double lung transplantation versus heart-lung transplantation. (*Reprinted from* Pinderski et al. [25] with *permission from Elsevier*)

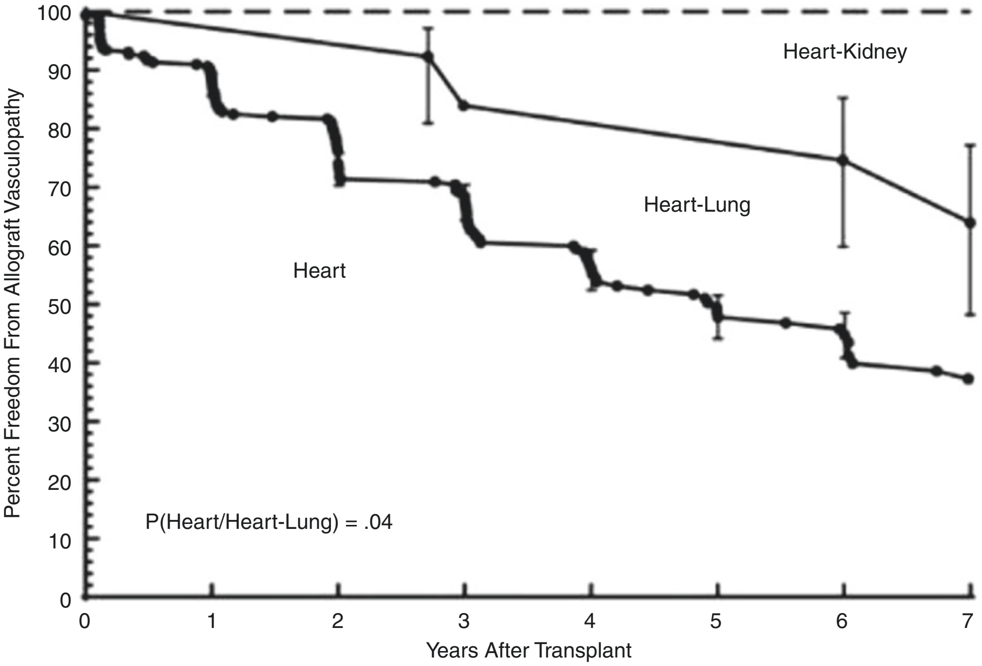

Fig. 71.9 Kaplan-Meier depiction of freedom from cardiac allograft vasculopathy after heart transplantation, heart-lung transplantation or heart/kidney transplantation. (*Reprinted from* Pinderski et al. [25] with *permission from Elsevier*)

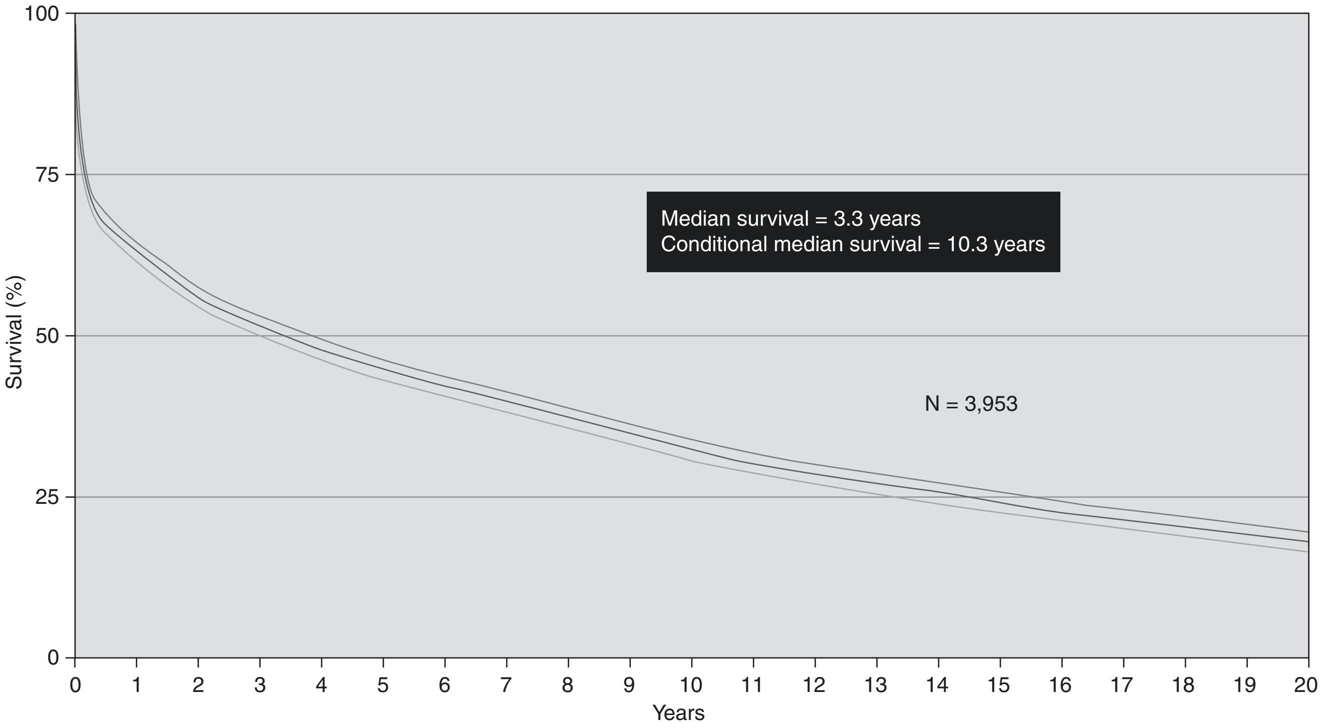

Fig. 71.10 Kaplan-Meier depiction of survival after adult heart-lung transplantation between January 1982 and June 2015; median survival = 3.3 years, conditional median survival = 10.3 years. (Modified from Chambers et al. [1] with *permission* from the International Society of Heart and Lung Transplantation)

Survival After Heart-Lung Transplantation

The median survival of patients after heart-lung transplantation based as reported by the ISHLT Registry is 3.3 years and the one-year conditional survival is 10.3 years (Fig. 71.10) [1]. The poor median survival is explained by the high early mortality. The causes of death in the ISHLT Registry (Fig. 71.11) have a time based distribution—death from graft failure and technical causes (most frequently

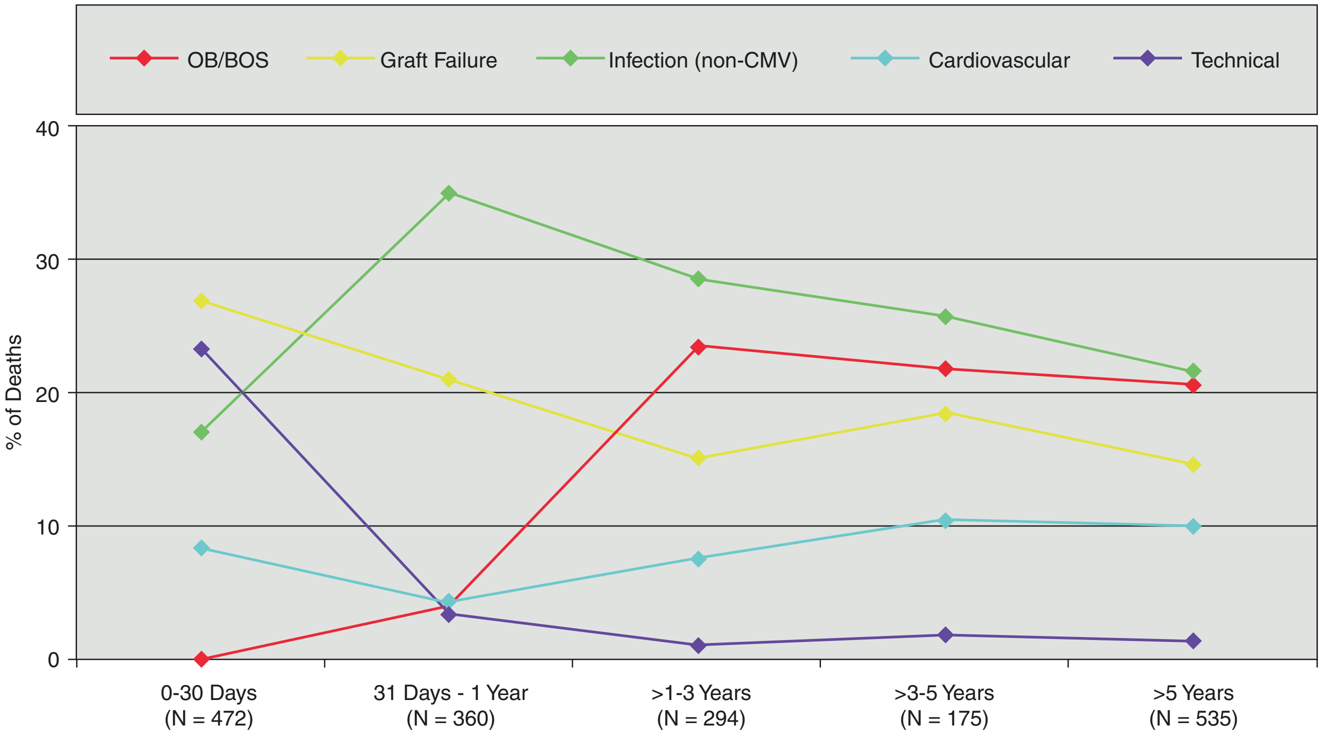

Fig. 71.11 Relative incidence of leading causes of death after adult heart-lung transplantation between January 1992 and June 2014; only known causes of death are included in the tabulation. *OB* obliterative bronchiolitis, *BOS* bronchiolitis obliterans syndrome, *CMV* Cytomegalovirus. (Modified from Chambers et al. [1] with *permission* from the International Society of Heart and Lung Transplantation)

bleeding) early after transplantation and the major late causes of death are CLAD and infection [1].

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Immunosuppression in Cardiac Transplantation

72

Yu Xie, Kevin W. Lor, and Jon A. Kobashigawa

High Yield Facts

- The goal of immunosuppression is to balance rejection prevention with side effects, toxicities, and infection.
- High-dose glucocorticoids, namely methylprednisolone and prednisone, were the first immunosuppressive agents to prevent and treat rejection.
- There are two main classes of induction agents: monoclonal antibodies and polyclonal antibodies.
- Maintenance therapy is a triple therapy consisting of a calcineurin inhibitor (CNI), an anti-proliferative agent and a glucocorticoid.
- Mycophenolic acid supplanted azathioprine as the primary antiproliferative agent because it improved heart transplant survival and decreased cardiac allograft vasculopathy (CAV) incidence.
- Tacrolimus decreases severe rejection episodes and improves overall survival compared to cyclosporine and is generally used as the primary CNI.
- Proliferation signal inhibitors can replace antiproliferative agents in cases of CAV, cytomegalovirus infection, donor specific antibody, or history of rejection.

Introduction

The first heart transplant was performed over 50 years ago on December 3, 1967 by Dr. Christiaan Barnard in South Africa. Initially, survival was poor due to infection and rejection. By 1980, survival had improved to ~50% at 5 years, primarily attributed to Dr. Norman Shumway. Immunosuppression consisted of high-dose corticosteroids and azathioprine [1]. In 1983, the FDA's approval of cyclosporine, the first calcineurin inhibitor (CNI), revolutionized transplantation and improved outcomes. Today, tacrolimus is the primary CNI and mycophenolate mofetil has replaced azathioprine. With these advances, the expected 1- and 10-year survival is over 90% and 50%, respectively [2, 3]. Along with improved immunosuppression, much of this success can also be attributed to better recipient-donor selection, advanced immunology understanding, and refined surgical techniques.

Despite these advances, post-transplant morbidity and mortality still potentially exist. Short-term morbidity and mortality includes primary graft dysfunction (PGD), ischemia-reperfusion injury, renal dysfunction, infection, and acute rejection. Long-term morbidity and mortality includes malignancy, graft failure, cardiac allograft vasculopathy (CAV), infection, and CNI-induced chronic kidney disease. CAV surveillance is currently monitored by angiogram with intravascular ultrasound (IVUS) [4], myocardial perfusion study, and cardiac MRI.

Goal of Immunosuppression

The goal of immunosuppression is to balance rejection prevention with side effects, toxicities, and infection. Therapeutic dose monitoring of immunosuppression and an understanding of drug-drug interactions is crucial. No standardized protocol exists and immunosuppression should be tailored to each patient's risk factors.

Medications for Desensitization Prior to Transplantation

The evaluation for pre-formed antibodies is critical to prevent rejection. Sensitization is defined by the presence of pre-formed HLA antibodies, based on a calculated panel reactive antibody (cPRA) algorithm. Desensitization prior to

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transplantation is dependent on antibody identification, activity, and apoptotic capability.

One desensitization strategy includes intravenous immune globulin (IVIg) and rituximab, which has been successful in kidney transplantation and adapted for use in heart transplantation [5]. Rituximab, an anti-CD20 monoclonal antibody, causes B-lymphocyte destruction. IVIg is a polyclonal antibody that blocks antibody function [6]. Another desensitization therapy is bortezomib with plasmapheresis. Bortezomib, which is FDA-approved for multiple myeloma, is a proteasome inhibitor that causes apoptosis in plasma cells. This therapy reduced cPRA in heart transplant patients who failed IVIg and rituximab [7].

Induction and Maintenance Therapies

Immunosuppression is classified into induction and maintenance therapies. Not all patients are given induction and their maintenance regimen depends on infection risk, rejection risk, and side-effects and toxicities. See Table 72.1 for more information on specific doses, protocols, and side-effects.

Induction Therapy

Induction is intense immunosuppression used in the first days after transplantation. Currently, about 50% of patients do not undergo induction [8]. Indications for induction

Table 72.1 Summary of immunosuppression medications used in heart transplantation

Category	Drugs	Doses	Side effects toxicities comments
Induction treatment	Methylprednisolone	Cross clamp: 500–1000 mg IV Day 1: 500 mg over 24 h Day 2: steroid taper	
	Rabbit Anti-Thymocyte Globulin (rATG, Thymoglobulin®)	1.5 mg/kg IV daily for 5 days, given with premedication (methylprednisolone IV, acetaminophen and diphenhydramine)	Can give 8–10 h infusion for first dose to minimize infusion-related reaction. Subsequent infusions can be 4–6 h as tolerated Central line preferred due to thrombophlebitis. Leukopenia, thrombocytopenia, infection
	Basiliximab (Simulect®)	20 mg IV at cross clamp day 0 and day 4	
Maintenance treatment	Prednisone	Rapid taper to 10–30 mg PO daily (or divided doses) for 1 month. Slow taper over 6–12 months to 5 mg PO daily and can further taper to withdrawal	At high doses: Mood instability, hyperglycemia, hypertension, myopathy, fluid retention gastric ulcers, and infection. Long term use: Adrenal insufficiency, osteoporosis, new onset diabetes, cataracts and acne
	CNI: Tacrolimus (preferred) cyclosporine	Initiate tacrolimus 0.5–2 mg PO/NG q 12 h, titrate to therapeutic level IV conversion is 20% of total daily PO dose, given as continuous infusion Initiate cyclosporine 25–200 mg PO/NG q 12 h, titrate to therapeutic level IV conversion is 33% of total daily PO dose given as continuous infusion or divided BID, given over a 2–6 h infusion	CYP P-450 drug-drug interactions (esp. azole, etc.) Hypertension, nephrotoxicity, hyperglycemia hyperlipidemia neurotoxicity and malignancy
	Antiproliferative agents: Mycophenolate mofetil (MMF, Cellcept®)—preferred mycophenolate sodium (MPS, Myfortic®) azathioprine (AZA)	Start MMF on day 1 at 1000–1500 mg PO/NG/IV q 12 h Conversion from MMF to MPS is MMF 250 mg = MPS 180 mg	Myelosuppression, nausea/vomiting CMV infection
	Proliferation signal inhibitors: Sirolimus (Rapamune®) everolimus (Zortress®)	Sirolimus 0.5–2 mg PO daily Titrate to therapeutic level Everolimus 0.5–1 mg PO q 12 h Titrate to therapeutic level	CYP P-450 drug-drug interactions (esp. azole, etc.) Check levels 5–7 days after initiation Nephrotoxicity (if used with CNI) Proteinuria Hypertriglyceridemia Fungal infection Thromboses Mouth ulcers Fluid retention

Table 72.1 (continued)

Category	Drugs	Doses	Side effects toxicities comments
Rejection treatment[a]	Prednisone	Mild and asymptomatic rejection: prednisone 1–3 mg/kg/day PO in divided doses × 1–3 days then rapid taper to 5–10 mg daily Severe or symptomatic rejection: methylprednisolone 500 mg q day × 3 days prednisone oral taper to 5–10 mg daily	Repeat EMBx in 2 weeks Likely not taper off prednisone
	rATG	For severe or symptomatic rejection: rATG 0.75–1.5 mg/kg IV × 5–7 days	MOA: Cytolytic therapy
	Intravenous immune globulin (IVIg)	For severe or symptomatic antibody mediated rejection: IVIg 1 g/kg × 2 days	MOA: Antibody inactivation Titrate infusion per local policy Infusion-related reactions Headache Flushing
	Plasmapheresis (PP)	For severe or symptomatic rejection: 5–7 days	MOA: Antibody removal Give before any therapeutic intravenous antibodies as PP removes them.
	Proliferation signal inhibitors: Sirolimus (Rapamune®) everolimus (Zortress®)	Sirolimus 0.5–2 mg PO daily Titrate to therapeutic level Everolimus 0.5–1 mg PO q 12 h Titrate to therapeutic level	Not initiated <3 months post-transplant Check levels 5–7 days after initiation
	Eculizumab	AMR: non-FDA approved Highly sensitized, cardiac standstill	MOA: Terminal complement inhibition Costly

AMR antibody mediated rejection, *CMV* cytomegalovirus, *EMBx* endomyocardial biopsy, *MOA* mechanism of action

[a] Belimumab, Epratuzumab and photopheresis are also therapies available for rejection that are used less frequently

include high rejection risk, such as sensitized or positive cross-match patients, and delaying CNI to allow for renal recovery [4, 9]. Some programs use induction for all patients.

There are two main classes of induction agents: monoclonal antibodies and polyclonal antibodies. Monoclonal antibodies include basiliximab (BAS) or Simulect® (interleukin-2 receptor antagonist, IL-2 RA) and alemtuzumab or Campath® (anti-CD52). IL-2 RA prevents IL-2 from binding to its receptor, which is important for T-lymphocyte proliferation and signaling. Anti-CD52 antibodies cause widespread T- and B-lymphocyte depletion [10]. Daclizumab (DAC), an IL-2 RA, and muromonab (OKT3), an anti-CD3, have been commercially discontinued in the U.S. Polyclonal antibodies include anti-thymocyte globulin (ATG) and anti-lymphocyte globulin (ALG). ATG is polyclonal IgG derived from rabbit (rATG, Thymoglobulin®) or equine/horse (eATG, ATGAM®). It has broad targets and effects [11–13] including functional T-lymphocyte consumption, cell-signaling and adhesion molecule modification [14], dendritic cell function impedance [15] and B-lymphocyte death [16].

In a retrospective cohort analysis among 9324 heart transplants from 2000 to 2011 with induction, ATG was associated with higher 5- and 10-year survival than basiliximab (77% vs. 82%, $p = 0.05$, and 64% vs. 67%, $p = 0.007$ respectively), despite having a higher baseline PRA [17]. ATG was also associated with decreased coronary plaque progression seen on angiogram with IVUS [18]. When using ATG, the CD2 or CD3 therapeutic goal is 25–50 cells/mm^3 or absolute lymphocyte count <100–200 cells/mm^3. Not all centers monitor ATG therapy and will administer fixed doses or adjusted doses based on toxicities such as infection, leukopenia or thrombocytopenia. IL-2 RA effectiveness is not monitored as it is a fixed regimen [4]. Despite the benefits of ATG, many centers are divided between ATG and IL-2 RA as their primary induction agent [3].

At our institution, the indications for ATG induction include: PRA > 10%, positive cross-match, multi-organ transplant, and renal insufficiency (serum creatinine >2 mg/dL, approximately). If a patient develops PGD, plasmapheresis is considered along with ATG. The criteria at other centers will vary.

Maintenance Therapy

Maintenance therapy is indefinite and helps prevent long-term rejection. Initial immunosuppression consisted of azathioprine and corticosteroids. The isolation of cyclosporine from the soil fungus *Tolypocladium inflatum* in 1976 and FDA approval in 1983 revolutionized transplantation by improving survival.

Most programs use triple therapy, which includes a CNI, an anti-proliferative agent and a glucocorticoid [19]. Triple therapy has better outcomes than dual therapy, although in select patients, corticosteroid withdrawal may confer the same rejection risk while reducing corticosteroid side effects and infection risk [20]. Figure 72.1 illustrates the mechanisms of action for immunosuppressants. Below is a more detailed description of each class of immunosuppressant in the standard triple therapy.

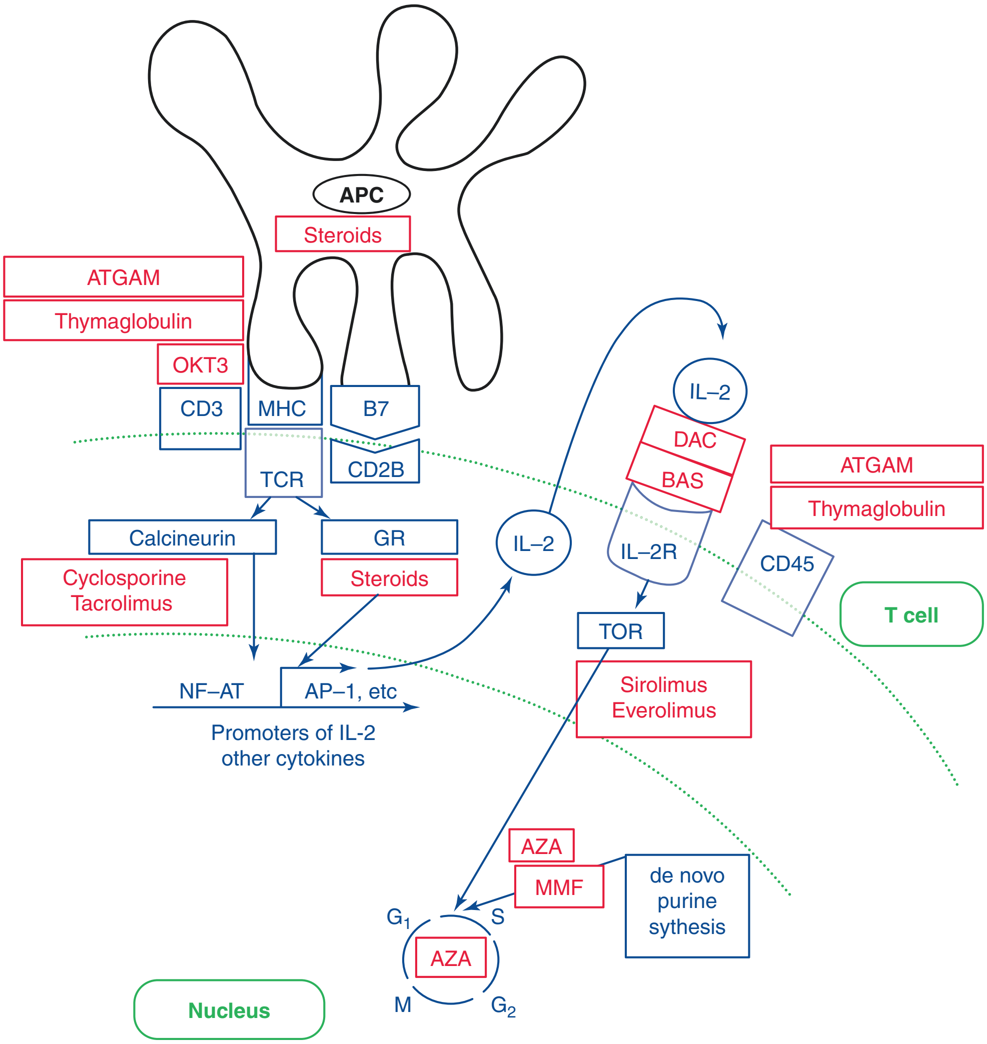
APC
Steroids
ATGAM
Thymaglobulin
OKT3
CD3
MHC
B7
TCR
CD2B
Calcineurin
GR
Cyclosporine
Tacrolimus
Steroids
NF–AT
AP–1, etc
Promoters of IL-2
other cytokines
IL–2
IL–2
DAC
BAS
IL–2R
ATGAM
Thymaglobulin
CD45
T cell
TOR
Sirolimus
Everolimus
AZA
MMF
de novo
purine
sythesis
G_1
S
AZA
M
G_2
Nucleus

Fig. 72.1 Mechanisms of immunosuppression drugs. (Reproduced with permission from [21])

Specific Immunosuppression Medications

Glucocorticoids

High-dose glucocorticoids, namely methylprednisolone and prednisone, were the first immunosuppressive agents to prevent and treat rejection. Their effects on the immune system are multifactorial. They bind to glucocorticoid receptors in the cytoplasm, which then bind to transcriptional factors in the nucleus, preventing or promoting gene regulation to decrease inflammation and T-lymphocyte response to foreign antigens [10, 19, 21]. Glucocorticoids also inhibit dendritic cells' presentation of antigens to T-lymphocytes [22].

Methylprednisolone 500–1000 mg IV is administered in the operating room at aortic cross-clamp removal [23]. Additional high doses of methylprednisolone IV are administered for the first day and tapered rapidly over the first week to a maintenance dose of prednisone 10–30 mg daily or divided doses and continued through the first month. A slow prednisone taper continues for 6–12 months until select patients are weaned off.

Side effects of glucocorticoids include hyperglycemia, hypertension, hyperlipidemia, myopathy, adrenal insufficiency, cataracts, gastric ulcers, osteoporosis, emotional lability, impaired wound healing, fluid retention, acne, and infection risk [20].

Antiproliferatives

Azathioprine

Azathioprine was the second immunosuppressive agent to gain widespread use. Azathioprine is converted into 6-mercaptopurine to disrupt purine synthesis. Side effects of azathioprine include leukopenia and bone marrow suppression [10]. A significant drug-drug interaction with allopurinol requires a 66–75% azathioprine dose reduction. Allopurinol inhibits xanthine oxidase, which degrades 6-mercaptopurine, resulting in increased 6-mercaptopurine toxicity [24].

Mycophenolic Acid

Mycophenolic acid supplanted azathioprine as the primary antiproliferative agent because it improved heart transplant survival and decreased CAV incidence [25]. Mycophenolate mofetil (MMF, Cellcept®) and mycophenolate sodium (MPS, Myfortic®) are rapidly converted into mycophenolic acid by plasma esterases. Mycophenolic acid reversibly inhibits inosine monophosphate dehydrogenase, which synthesizes guanine for T- and B-lymphocytes [26].

MMF is more commonly used as it has oral and intravenous forms, and is cheaper. MPS is enteric-coated and may have less gastrointestinal distress than MMF [27]. MMF 1000–1500 mg IV/PO/NG q12h is usually initiated on POD0. Mycophenolic acid is dosed to patient tolerance of gastrointestinal and pancytopenic side effects without regard to drug levels [4].

Calcineurin Inhibitors

Cyclosporine binds to cyclophilin and tacrolimus binds to FK Binding Protein (FKBP-12). They both inhibit the actions of calcineurin. Calcineurin dephosphorylates nuclear factor of activated T-cells (NFAT), which binds and inhibits the promotor region of the IL-2 gene. IL-2 is an important cytokine that stimulates proliferation of additional T- and B-lymphocytes in response to foreign antigens [28–30].

Tacrolimus decreases severe rejection episodes and improves overall survival compared to cyclosporine and is generally used as the primary CNI [31]. For patients with renal dysfunction, tacrolimus initiation can be delayed until completion of ATG therapy to avoid further kidney insult [32].

Initial tacrolimus and cyclosporine doses range from 0.5 to 2 mg PO/NG q12h and 25–200 mg PO/NG q12h, respectively. Daily adjustments based on trough levels are necessary to evaluate efficacy and minimize toxicity. CNI dosing is subject to inter-patient and intra-patient variability. Cyclosporine goal troughs range from 275 to 375 ng/mL and tacrolimus goal troughs range from 10 to 15 ng/mL for the first 1–2 months post-transplant. For months 2–6, cyclosporine troughs are 200–350 ng/mL and tacrolimus troughs are 8–12 ng/mL. After 6 months, cyclosporine and tacrolimus troughs are 150–250 ng/mL and 5–10 ng/mL, respectively [4]. Further adjustment may be needed due to renal toxicity, severe infection, or malignancy [4, 19, 21].

The primary CNI side effects are nephrotoxicity, neurotoxicity (seizure, headache, tremor), metabolic changes (hypercholesterolemia, hypertension, diabetes, hyperkalemia, hypomagnesemia), and cosmetic changes. Tacrolimus can cause alopecia, whereas cyclosporine can cause hirsutism and gingival hyperplasia. Malignancy is also a long-term concern [33, 34].

Proliferation Signal Inhibitors

Sirolimus (Rapamune®) and everolimus (Zortress®) both bind to FKBP-12 which inhibits mechanistic Target of Rapamycin (mTOR). This impairs the cell cycle pathway for cell growth and replication [35, 36]. Therapeutic sirolimus and everolimus levels range from 4 to 12 ng/mL and 3–8 ng/mL, respectively [4]. Levels are drawn before the next administered dose. As the half-life of sirolimus and everolimus is 60 h and 25 h, respectively, steady state levels are not achieved for 1–2 weeks.

Proliferation signal inhibitors (PSI) can replace antiproliferative agents in cases of CAV, CMV infection, donor specific antibody (DSA), or history of rejection [25, 37–39]. They may also be beneficial to replace either CNI or antiproliferative agents in malignancy [39, 40]. In the SCHEDULE trial, comparing early initiation of everolimus versus cyclosporine on the background of MMF and a corticosteroid, everolimus had decreased intimal medial thickening and fewer CAV diagnoses at 3-years, with similar sternal wound healing. The SCHEDULE trial also showed that everolimus patients had improved serum creatinine level, but increased rejection [41–43]. In select patients with CNI-induced nephrotoxicity, a PSI can replace the CNI [4].

Due to observed increases in infection, wound dehiscence and pericardial effusions, PSI are not used within the first 3 months post-transplant [4, 25, 37]. Other side effects of PSI include leg edema, deep vein thrombosis, mouth ulcers, fungal infections, proteinuria, and hypertriglyceridemia [4]. Up to 38% of patients may not tolerate switching to a PSI due to side effects [44]. One rare, but serious side effect of PSI is pneumonitis [45].

Which Regimen Is Superior?

Standard Triple Therapy

Tacrolimus is the cornerstone of standard triple therapy. In the 3-Arms Trial comparing Tacrolimus + Sirolimus + GC vs. Cyclosporine + MMF + GC vs. Tacrolimus + MMF + GC, among 334 transplant patients over 28 centers, there was a strong trend toward decreased ≥ ISHLT grade 3A rejection or hemodynamic compromise rejection in both tacrolimus groups compared to the cyclosporine group (TAC/SIRO 35.1%, TAC/MMF 42.1% and CYA/MMF 59.6%). Furthermore, the TAC/MMF combination had improved tolerability compared to TAC/SRL [37].

Corticosteroid Withdrawal

In select patients, steroids can be withdrawn by the first year through a slow wean [4]. However, patients who are at higher

Table 72.2 Common heart transplant regimens

Indication	Regimens
Standard triple therapy	CNI + MMF + GC
Steroid withdrawal therapy (*>1 year post-transplant AND low-risk of rejection*)	CNI + MMF
History of rejection, DSA or CAV (*Strongest maintenance regimen*)	CNI + PSI + GC
CMV infection or malignancy	CNI + PSI
Renal sparing protocol (*CNI free*)	PSI + MMF ± GC

CAV cardiac allograft vasculopathy, *CMV* cytomegalovirus, *CNI* calcineurin inhibitor, *DSA* donor specific antibody, *MMF* mycophenolate mofetil, *GC* glucocorticoid, *PSI* proliferation signal inhibitors

Table 72.3 Calcineurin inhibitor (CNI) drug interactions

Drugs that increase CNI levels	Drugs that decrease CNI levels
Cimetidine Ciprofloxacin Clarithromycin Diltiazem Erythromycin Fluconazole Ketoconazole Metoclopramide Nicardipine Posaconazole Ranitidine Verapamil Voriconazole	Cholestyramine Ethambutol Ethanol Isoniazid Nafcillin Octreotide Phenobarbital Phenytoin Rifampin

risk for rejection, including those who are sensitized, have donor specific antibody (DSA), or history of rejection should typically be maintained on a triple-drug therapy with low-dose corticosteroids [34, 46, 47].

Renal Sparing

Due to CNI-induced chronic renal toxicity, the CNI can be switched to a PSI. However, rejection risk can increase [28, 41]. One method to convert to a PSI is to halve the dose of the CNI while simultaneously initiating the PSI to reduce rejection risk. The CNI is discontinued when the PSI level is therapeutic. See Table 72.2 for common immunosuppression regimens used in heart transplantation.

The JHLT 2010 guideline gives a summary of some of the published data on immunosuppression comparison in heart transplant patients [4].

Drug-Drug Interactions

Given the drug-drug interaction of CNI with statins, reduced dose for statins is recommended. See the JHLT 2010 guideline for a comprehensive list [4].

CNI and PSI are heavily dependent on the cytochrome P450 enzyme metabolic system, specifically subtype 3A4 [48, 49]. Metabolic activity is dependent on genetics also, as African Americans tend to require higher doses of CNI due to increased activity of CYP3A4, while also utilizing subtype CYP3A5 when metabolizing tacrolimus [50, 51]. Many drugs inhibit the CYP3A4/5 enzymes, causing an increased CNI or PSI level if used concomitantly. For example, the azole antifungals can increase tacrolimus concentrations two- to ninefold. Other drugs induce CYP3A4/5 enzymes, causing a significant decrease in CNI or PSI level if used concomitantly [52]. See Table 72.3 for list of common medications known to affect CNI levels.

Furthermore, herbal medications are discouraged due to lack of data on drug interactions [52]. Grapefruit juice is also an inhibitor of CYP3A4/5 [52].

Medications for Rejection

Rejection

There are two types of acute rejection: acute cellular rejection (ACR) and antibody mediated rejection (AMR). Rejection is most common within the first 12 months post-transplant, and if untreated, is associated with increased morbidity and mortality [53]. Rejection can be diagnosed clinically, on imaging, and/or by endomyocardial biopsy (EMBx). EMBx concordance rate among independent pathologists is moderate (71%, in CARGO II study) [54] and confounded by sampling error. Understandably, there are cases of biopsy-negative clinical rejection. See Table 72.4 for treatment algorithms for rejection.

Endomyocardial Biopsy (EMBx) and Non-invasive Methods to Screen for Rejection

No standardized protocol exists for the frequency of surveillance with EMBx, but the frequency decreases significantly after the first year. There is an increasing use of non-invasive methods such as gene expression profiling blood tests and biopsy samples [55] to better evaluate for rejection, given there is only modest concordance among pathologists on EMBx samples [54].

Acute Cellular Rejection

The treatment for ACR depends on severity. The first line of treatment for clinically significant ACR or asymptomatic

Table 72.4 Treatment algorithms for rejection[a]

Type of rejection	Asymptomatic		Reduced LVEF	Heart failure/shock
Acute Cellular Rejection (ACR) CD4 and CD8 T cells target donor HLA → cytotoxic T cells → cell damage and death	Target higher CNI levels Oral steroid bolus + taper Switch MMF → PSI		Oral steroid bolus/taper or IV pulse steroids	IV pulse steroids ATG Plasmapheresis (before ATG dose) IVIg Inotropic therapy IV heparin ± Eculizumab IABP/ECMO
Antibody Mediated Rejection (AMR) B cell activate → plasma cells → produce Ab against HLA → complement-dependent cytotoxicity	No/low level DSA	Observe	Oral steroid bolus/taper or IV pulse steroids ± IVIg	
	High level DSA	Oral steroid bolus/taper IVIg ± rituximab	IV pulse steroids IVIg ± rituximab Consider ATG	

Ab antibody, *ATG* antithymocyte globulin, *CNI* calcineurin inhibitor, *DSA* donor specific antibody, *ECMO* extracorporeal membrane oxygenation, *HLA* human leukocyte antigen, *IABP* intra-aortic balloon pump, *IVIg* intravenous immunoglobulin, *LVEF* left ventricular ejection fraction, *MMF* mycophenolate mofetil, *PSI* proliferation signal inhibitor

[a] Adapted from [72, 73]

high-grade biopsy proven ACR is corticosteroids (usually methylprednisolone 500–1000 mg IV daily, for 1–3 days). Additionally, ATG (rATG preferred) 0.75–1.5 mg/kg for at least 5 days should be considered for severe cases. The patient should be in the ICU if there is hemodynamic compromise given the rapid deterioration these patients may experience. A long-term plan to intensify or switch maintenance immunosuppression should be discussed. For asymptomatic moderate grade biopsy proven ACR, there is the option to treat with oral or intravenous steroids (for example, prednisone 1–3 mg/kg/day oral for 3–5 days).

Antibody Mediated Rejection

While the prevalence of ACR has dropped significantly over the last 20 years, the prevalence of AMR has remained relatively stable [53]. Risk factors for AMR include female sex, younger age, and African American race [56]. AMR, even when asymptomatic, increases risk of CAV [57], which in turn increases mortality [58]. According to the JHLT AMR consensus, AMR is now defined by a combination of histology and immunopathology criteria [53]. Immediate treatment of severe AMR includes ATG, IVIg, and plasmapheresis. Complement inhibitors, although not FDA approved and costly, may also be considered in patients with hemodynamic compromise [59].

Some future possible directions for AMR treatment include belimumab and epratuzumab [60]. Once a patient has completed the acute treatment for symptomatic AMR and still has persistently low EF, restrictive physiology, or new DSAs, s/he is a potential candidate for outpatient photopheresis, which is 18 sessions over 6 months.

Cardiac Allograft Vasculopathy

CAV, monitored on angiogram via IVUS, is thought to be the downstream effect from ischemia-induced injury to the donor endothelial cells, activation of the immunological cascade, upregulation of cytokines, and intimal hyperplasia [61, 62]. It is considered a form of chronic rejection and associated with higher incidence of death and graft loss [63]. CAV is treated or prevented by switching from an antiproliferative agent to a PSI [64–66], adding a statin [67, 68], adding vitamin C and E supplementation [69–71], and percutaneous coronary intervention (PCI).

Future Directions

Ongoing studies in transplantation are evaluating the efficacy of novel immunosuppression, including eculizumab (Soliris®, a human monoclonal antibody against complement C5a component), tocilizumab (Actemra®, an IL-6 receptor inhibitor) and imlifidase (IdeS, experimental in ongoing clinical trials, an IgG-degrading enzyme of Streptococcus pyogenes that cleaves IgG).

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Complications of Heart Transplantation

73

Mayooran Shanmuganathan and Owais Dar

High Yield Facts
- Main early complications include primary graft failure, infection and rejection.
- Main late complications include cardiac allograft vasculopathy, renal failure, malignancy, late graft failure and rejection.
- Medication related adverse effects such as hypertension, osteoporosis, diabetes and hyperlipidaemia are common.
- The role of the transplant cardiologist is careful optimisation of transplant immunosuppressant medication to minimise risk of rejection whilst also minimising the risk of infection and medication related adverse effects.
- Median life expectancy of adult heart transplant recipients is 10.7 years

Introduction

Advanced heart failure is associated with a very poor prognosis and quality of life. Heart transplantation (HTx) provides the best mid- to long-term survival and symptom relief for eligible patients. Currently the median life expectancy is around 10.7 years and for patients who survive the first-year post-transplant median survival is 13.3 years [1] (Fig. 73.1). Many factors limit survival after HTx. Our understanding of the frequency and importance of many of these complications comes from the International Society of Lung and Heart Transplant (ISHLT) Registry. This holds detailed information on over 120,000 adult heart transplant recipients from 472 transplant centres across the world and has now published its 34th report in 2017. Largely using data from this registry, this chapter will provide the reader with information on the factors that contribute to morbidity and mortality in HTx survivors.

Background

Transplant recipients are committed to a programme of lifelong immunosuppression medication to prevent rejection. Rejection can present acutely or more chronically. Acute rejection requires immediate treatment without which it could lead to serious harm or even death. Chronic rejection presents itself in a more indolent way and clinically can become apparent as a gradual decline in graft function over time. This can be due to coronary artery disease within the transplanted heart; it is also known as graft vascular disease or cardiac allograft vasculopathy (CAV) and will be discussed in more detail later in the chapter. Alternatively, it manifests as a reduction in graft function with no obvious identifiable cause.

Most HTx recipients are maintained on triple immunosuppressive therapy namely: (1) a calcineurin inhibitor (e.g. tacrolimus or cyclosporin), (2) mycophenolate mofetil and (3) prednisolone. These drugs are associated with long-term side effects such as hypertension, hyperlipidaemia, diabetes, renal failure, malignancy. The challenge faced by transplant cardiologists is to minimise immunosuppression thereby preventing morbidity and mortality associated with these side effects whilst preventing the consequences of acute and chronic rejection discussed above. Consequently, most patients are weaned of steroids by the end of the first year after HTx and are maintained on dual therapy (tacrolimus/cyclosporin and mycophenolate). The choice between the

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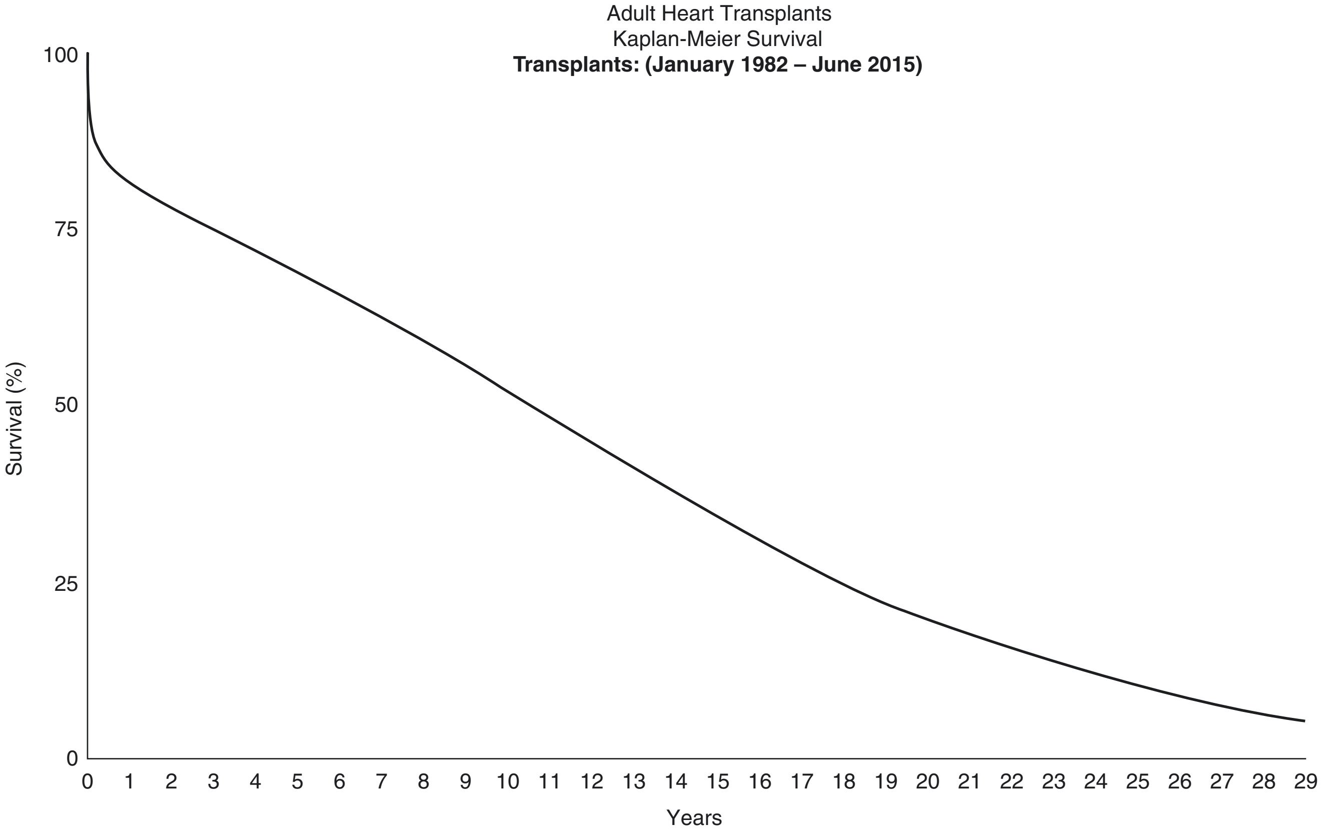

Fig. 73.1 Survival after heart transplantation in adult patients

use of tacrolimus and cyclosporin is largely centre specific. However, most centres nowadays prefer tacrolimus due to evidence suggesting tacrolimus is associated with marginally better renal function, better blood pressure control and reduced rejection rates [2]. However, unlike cyclosporine, tacrolimus is associated with the development of diabetes.

ISHLT registry data suggests the leading cause of death changes over time. In the early post-operative period graft failure and multi organ failure, followed by infection and then rejection are the leading causes of death. Although these three causes of death remain a threat over time their relative importance diminishes after the first year of transplant. Beyond the 3-year follow-up period, CAV, malignancy and renal failure become a relatively bigger issue as depicted in Fig. 73.2 and Table 73.1.

Early Complications

Primary Graft Dysfunction (PGD) or Primary Graft Failure (PGF)

Graft failure is the commonest cause of death in the first 30 days (45%) [3]. Although a universally accepted definition was lacking until recently, it is now defined as ventricular dysfunction which may involve the left (PGD-left), right (PGD-right) or both the ventricles and occurs within 24 h of heart transplantation. It should be distinguished from secondary causes of graft failure such as hyperacute rejection, pulmonary hypertension and surgical complications such as bleeding [4].

Several factors increase the risk of graft failure. They can be categorised into donor, recipient and operation related factors. Donor and procedural risk factors include ischaemic time more than 6 h, donor-recipient size mismatch and Human leucocyte antigen (HLA) mismatch. Acute ischaemia-reperfusion injury with myocardial stunning due to the various insults on the donor heart is one of the possible reasons for the development of PGD [5, 6]. Recipients with congenital heart disease, hypertrophic cardiomyopathy, pulmonary hypertension, mechanical circulatory support or with a previous heart transplant are at higher risk of PGD.

PGD usually manifests as hypotension and cardiogenic shock requiring circulatory support (inotropes, vasopressors or use of mechanical assist device). It is diagnosed with echocardiography and cardiac output studies (cardiac index <2 L/min/m^2, CVP > 15 despite adequate filling, PCWP > 20 mmHg). It is treated with inotropes, vasopressors and, if needed, with mechanical assist devices. Extra Corporeal Membranous Oxygenation (ECMO) appears to be the preferred method in severe PGD and may even be inserted immediately after surgery when coming off cardiopulmonary

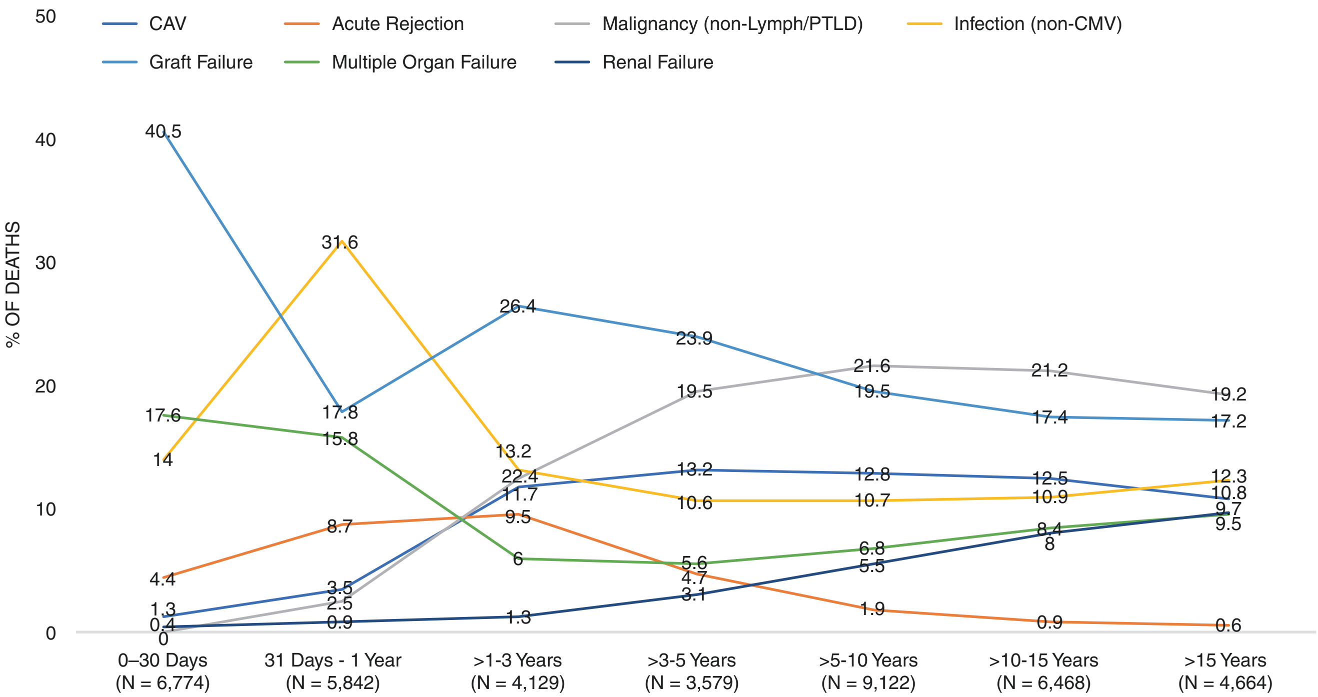

Fig. 73.2 Relative incidence of leading causes of death in adult transplant recipients in different time periods after hear transplantation surgery (January 1994–June 2016). (Source: Lund et al. 2017 [1])

Table 73.1 Causes of death in adult heart transplants between Jan 1994–June 2016[a]

Cause of death	0–30 days	>1–3 years	>5–10 years	>10–15 years	>15 years
Cardiac allograft vasculopathy	1.3%	11.7%	1169 (12.8%)	807 (12.5%)	502 (10.8%)
Acute rejection	4.4%	9.5%	1.9%	0.9%	0.6%
Lymphoma	0%	2.4%	3.3%	2.7%	2.1%
Malignancy, Other	0%	12.4%	21.6%	21.2%	19.2%
CMV	0%	0.5%	0.1%	0.1%	0
Infection, non-CMV	14.0%	13.2%	10.7%	10.9%	12.3%
Graft failure	40.5%	26.4%	19.5%	17.4%	17.2%
Technical	7.1%	0.8%	1.0%	1.3%	1.3%
Other	4.3%	7.8%	7.6%	6.6%	7.4%
Multiple organ failure	17.6%	6.0%	6.8%	8.4%	9.5%
Renal failure	0.4%	1.3%	5.5%	8.0%	9.7%
Pulmonary	2.8%	4.1%	4.4%	4.5%	4.5%
Cerebrovascular	7.5%	3.9%	4.7%	5.5%	5.5%

CMV cytomegalovirus

[a]Adapted from the ISHLT registry 2017 report. Lund et al. 2017 [1]

bypass. Hearts usually recover within 3 days on ECMO, but some have noted recovery as late as 7 days after surgery [7]. Re-do transplantation for severe PGD may be indicated in patients if risk factors are minimal.

Pulmonary Hypertension and Right Ventricular Dysfunction

Pre-transplant pulmonary hypertension increases the risk of death and graft failure due to the risk of right ventricular (RV) failure post transplantation [8]. Thus, careful patient selection is essential, and most centres would consider the presence of severe pulmonary hypertension (pulmonary vascular resistance >5 Wood units) to be a contra-indication for transplantation. Treatment of this complication involves inotropic support to improve RV function (milrinone, dobutamine, epinephrine or enoximone) and the use of vasodilators which can reduce pulmonary hypertension (e.g. nitroglycerine, sodium nitroprusside, prostaglandins, inhaled nitric oxide or sildenafil). Preload should be optimised with diuretics and or haemofiltration whilst maintaining the heart in normal rhythm and rate as well as correcting hypoxia and metabolic disturbances [8]. In cases of refractory RV failure, RV assist devices (RVAD) or ECMO therapy should be considered.

Rejection

Hyperacute rejection is rare nowadays. To prevent rejection and improve organ compatibility pre-transplant screening of blood group, HLA antibodies and virtual cross match of the donor heart antigens and the recipient's serum antibodies are routinely carried out. Hyperacute rejection tends to occur early on i.e. as cardiopulmonary bypass is weaned off in theatre.

Although around a quarter of patients will have evidence of rejection on their surveillance endomyocardial biopsies in the first-year post transplant only around 13% of patients can expect to be treated for rejection [1]. This can manifest itself as asymptomatic drop in cardiac graft function and is usually picked up by surveillance echocardiography as reduced left ventricular ejection. Less frequently it can present more overtly with the development of new heart failure symptoms, arrhythmias, cardiogenic shock requiring either inotropes or mechanical circulatory support [9]. The diagnosis is aided by the analysis of endomyocardial biopsy and by the detection of newly formed antibodies against the donor heart. Close collaboration with the immunologist and histopathologist is required. Treatment options include intravenous high dose corticosteroids, anti-lymphocyte antibodies, IV immunoglobulins and plasmapheresis.

Non-cytomegalovirus Infections

Although a risk at any time after transplant, non-cytomegalovirus (CMV) infections is a serious issue in the first 12 months after transplant. These account for 14% of deaths in the first month after transplant and 31% of deaths between the second month and 12th month [1]. Hospital acquired infections due to mechanical ventilation, catheter tubes and surgical wounds are most common in the first month after transplant. Infections can be caused by activation of latent infections with any one of viruses, protozoans, bacteria or fungi [10]. Trimethoprim/sulfamethoxazole (Septrin) is given in many centres as prophylaxis against Pneumocystis infections and antiviral agents such as valganciclovir are also given to prevent CMV infection. Infections are treated in a conventional manner.

Cytomegalovirus Infections

Cytomegalovirus (CMV) infections usually develop a month after transplant and the incidence is the highest in the first 3 months. Prophylactic valganciclovir is given at varied doses depending on perceived risk of infection and may reduce the incidence of CMV infections by 50% and attenuate the severity of symptoms. Patients are routinely screened over the first 6 months for CMV infection using polymerase chain reaction (CMV DNA PCR). In acute CMV infections, patients often present with nonspecific febrile illness. It can also result in tissue invasive pneumonia, gastro intestinal ulcers, hepatitis and retinitis and in the long term thought to cause more opportunistic infections and allograft failure. Treatment is either high dose oral valganciclovir or IV valganciclovir. Whilst it is a major cause morbidity, mortality from CMV infections is low at 0–1% at any time point after transplant [1].

Surgical Complications

Common early surgical complications after heart transplantation include pericardial effusion (in 61% of patients), tamponade (5.4%), post-operative arrhythmia (41%), mediastinal bleeding (8.4%), vasoplegic syndrome (11–54%) and sternal wound infections (2–8.8%) [11–14].

Acute Kidney Injury (AKI) Requiring Haemofiltration

AKI after heart transplantation is very common and is multifactorial. Graft ischaemic time, high troponin release after transplant (a marker of graft preservation ineffectiveness), blood loss, hypotension, sepsis and use of calcineurin inhibitor (CNI) immunosuppression are some of the post-operative factors that contribute to AKI. A single centre study of 307 patients showed that 14% of patients develop at least 50% reduction in estimated glomerular filtration rate (eGFR) and 6.1% need renal replacement therapy (RRT) [15]. Another single centre study of 346 patients showed a 16% use of RRT within the first week after transplantation [16]. Only severe AKI requiring RRT was shown to be an independent risk factor for in-hospital mortality [17].

Late Complications

Renal Dysfunction

Renal dysfunction is a common morbidity in patients after heart transplantation. It is caused by multiple factors including use of CNI immunosuppression, pre-transplant renal impairment, older age, female sex and diabetes [18, 19]. Five years after transplantation 13.8% of survivors have significant renal dysfunction defined as creatinine >2.5 mg/dl. Up to 4.6% and 10.5% of patients require chronic dialysis or renal transplant at 5 and 10 years respectively. Preventing renal failure is difficult in this population but switching from CNI based immunosuppression to sirolimus based immunosuppression may be helpful. Additionally, better control of traditional risk factors such as diabetes, hypertension and hypercholesterolemia should be adopted. Renal transplant offers 43% greater chance of survival compared to dialysis in heart transplant patients [20].

Cardiac Allograft Vasculopathy (CAV)

The cardiac transplantation registry database (CTRD) in 1999 showed that 42% have angiographic evidence of CAV 5 years after transplant but only 7% had severe CAV. Severe CAV is defined as coronary artery luminal stenosis >70% in either the left main stem or two major arteries or three branch arteries in all three major territories. Two thirds of the severe CAV patients died or needed a re-do heart transplantation [21]. The recent ISHLT registry data in 2017 shows that CAV prevalence is decreasing but still contributes to 11–13% of mortality at any given time 1 year from cardiac transplantation (Table 73.1). Due to the transplanted heart being mostly denervated, patients experience silent myocardial ischaemia and infarction and reduction in graft function. Thus, regular monitoring for development of CAV with invasive coronary angiography is recommended at least 1 year after transplant and then biennially.

CAV occurs because of the long exposure of the donor heart to low level attack from the recipient's immune system. Treatment of CAV largely rests on the better control of traditional cardiovascular risk factors as in any other non-transplant patient with coronary artery disease. In addition, attention needs to be paid to improving immunosuppression. There is some evidence that immunosuppressants in the class known as mammalian target of rapamycin (mTOR) inhibitors e.g. sirolimus and everolimus are better at controlling the progression of CAV. In some centres, patients with worsening CAV are switched from CNI therapy to an mTOR inhibitor. In appropriate situations percutaneous revascularisation is needed and helpful. It is however associated with higher restenosis rates than in a non-transplant cohort. CAV manifests itself differently to conventional coronary artery disease and typically presents as more diffuse disease as opposed to discrete stenoses. Partly because of this bypass surgery is associated with a very high mortality and is rarely performed. In such circumstances the only viable option is re-do heart transplantation.

Malignancy

Malignancy poses a significant mortality risk in the heart transplant recipients after 1 year. After 3 years from heart transplant, 19–21% of deaths are due to malignancy (Table 73.1) and these are mostly caused by post-transplant lymphoproliferative disorder (PTLD) and lung cancer. The most common cancer is squamous cell carcinoma, occurring in 18% of all adult heart transplant patients. It is purported that immunosuppressive therapies induce cancer via inhibition of endogenous anti-tumour responses. Screening for malignancy with chest radiography and dermatologist evaluation is essential. Once cancer is diagnosed, consideration should be given to reduce immunosuppression.

Other Chronic Complications

Heart transplant recipients often have increased incidence of hypertension, diabetes, hyperlipidaemia and osteoporosis. This can be attributed to the immunosuppressive medications including steroid therapy. Thus, vigilant monitoring and treatment with anti-hypertensive agents, statins, vitamin D, calcium supplements and bisphosphonates are initiated soon after transplant especially for the duration of steroid therapy. Anti-hypertensive therapy may be weaned down over time with the tapering of CNI dosage. Statin therapy is usually continued indefinitely as it improves survival and is associated with reduced incidence of CAV and cellular rejection [22]. Diabetes remains a risk throughout a transplant patient's lifetime due to intermittent steroid use, associated weight gain and use of CNI such as tacrolimus.

Conclusion

Median survival post-transplant is 10.7 years. Causes of death post-transplant vary over time. Graft failure, infection and rejection are main causes of morbidity and mortality in the first-year post-transplant. In addition to these complications the long-term survival is limited by the development of renal failure, CAV and malignancy. Close vigilance for complications and careful management of transplant immunosuppressant medication is vital to maximize survival and minimize morbidity.

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Part VI

Miscellaneous Cardiovascular Disorders

Cardiac Tumors

74

Maria Romero and Renu Virmani

High Yield Facts

- Cardiac tumors are rare and majority of these are benign.
- Cardiac myxoma represents the majority of benign cases.
- Metastatic tumors are the most common tumors of the heart.
- Majority of cardiac tumors present with some combination of congestive heart failure, arrhythmia, or thromboembolism. The signs and symptoms are related to the precise location within the heart, tumor size, and chamber of involvement.
- Cardiac tumors are diagnosed non-invasively by echocardiography, magnetic resonance imaging and computed tomography.
- Surgical resection is usually performed for primary lesions with excellent prognosis in the case of benign tumors.

Incidence

Mostly benign cardiac tumors are rare, with an autopsy incidence of primary tumors estimated between 0.001% and 0.3% [1], while metastatic tumors comprise the most common tumors of the heart. The reported ratio of cardiac metastasis to primary cardiac tumors ranges from 100/1 to 1000/1 [2–4]. Cardiac myxoma represents the majority of these neoplasms [5]. The relative frequency of cardiac tumors that are surgically removed and their mean ages at presentation are presented in Table 74.1.

Table 74.1 Incidence of primary cardiac tumors[a] by mean age at presentation[b]

Tumor type	%	Mean age at presentation
Rhabdomyoma[c]	2	33 weeks
Fibroma[c]	2	13 years
Rhabdomyosarcoma	<1	15 years
Hemangioma	1	31 years
Paraganglioma	<1	39 years
Sarcoma (angiosarcoma)	4	40 years
Sarcoma (myofibroblastic)	9	41 years
Myxoma	76	50 years
Papillary fibroelastoma	5	59 years
Lipomatous hypertrophy/lipoma	<1	64 years
Primary lymphoma	1	67 years

Modified from Burke A, Jeudy J Jr., Virmani R, et al.: Cardiac tumours: an update. Heart 2008:94;117–123

[a] Based on 250 tumor resections from five institutional surgical series

[b] Based on authors' experience of consultation material

[c] Incidence of pediatric tumors varies by institutional setting—that is, proportion of pediatric patients

Classification

There is no specific classification or grading scheme for malignant cardiac tumors. The classification and grading system outlined in the World Health Organization (WHO) classification of Tumors of Soft Tissue and Bone is currently applied as the vast majority of malignant heart tumors are sarcomas with extracardiac counterparts, which are similar, if not identical, histologically (Table 74.2).

Clinical Symptoms

Cardiac tumors usually present with congestive heart failure, arrhythmia or thromboembolism with over 50% of cases due to a large intracavitary mass; depending upon the chamber of involvement they may result in either backward or forward low-output heart failure [6]. The signs and symptoms are related to the precise location within the heart, tumor size, and chamber of involvement (Table 74.3).

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Table 74.2 WHO histologic classification of tumors of the heart

Benign tumors and tumor-like lesions	Malignant tumors	Pericardial tumors
Rhabdomyoma Histiocytoid cardiomyopathy Hamartoma of mature cardiac myocytes Adult cellular rhabdomyoma Cardiac myxoma Papillary fibroelastoma Hemangioma Cardiac fibroma Inflammatory myofibroblastic tumor Lipoma Cystic tumor of the atrioventricular node	Angiosarcoma Epitheloid hemangioendothelioma Malignant pleomorphic fibrous histiocytoma (MFH)/ Undifferentiated pleomorphic sarcoma Fibrosarcoma and myxoid fibrosarcoma Rhabdomyosarcoma Leiomyosarcoma Synovial sarcoma Liposarcoma Cardiac lymphomas Metastatic tumors	Solitary fibrous tumor Malignant mesothelioma Germ cell Tumors Metastatic pericardial tumors

Modified from Tumors of the Lung, Pleura, Thymus and Heart. Eds Travis WD, Brambilla E, Muller-Hermelink H-K, Harris CC. World Health Organization Classification of Tumor. WHO Press, Geneva, Switzerland. 2004. P 250

Reactive Cardiac Masses and Pseudotumors

Mural Thrombi

Endocardial thrombi in the atria are generally left sided and the majority of mural thrombi occur in association with underlying heart disease [7]. Mural thrombi are occasionally removed surgically, and are often clinically and pathologically misdiagnosed as myxomas. Left atrial thrombi are frequently associated with mitral valvular disease, especially mitral stenosis, and thrombi occur in either atrium in patients with atrial fibrillation. Ventricular thrombi likewise may form with decreased or abnormal ventricular contractility, particularly in patients with cardiomyopathy or ischemic heart disease, especially at sites of transmural infraction. In patients with known cardiac disease, mural thrombi are readily diagnosed by imaging studies and biopsy or resection is only rarely performed.

Mural thrombi in the absence of heart disease occur in any chamber, but are most common in the right atrium. Histologically, organizing thrombi are characterized by layers of degenerating blood cells, fibrin and a margin of granulation tissue with varying degree of fibrosis depending on age of the thrombus. The differential diagnosis of mural thrombus includes primarily cardiac myxoma and the site of attachment helps make this distinction.

Table 74.3 Cardiac symptoms by tumor type

Benign tumors
Cardiac myxomas
• Obstructive cardiac symptoms: left atrial myxoma—prolapse into (by various degrees) mitral orifice, LVOT obstruction—shortness of breath or syncope or progressive cardiac failure
• Embolic symptoms
• Constitutional symptoms
Papillary fibroelastoma
• Embolic symptoms of obstruction of coronary or cerebral circulation as 80–90% located on the aortic or mitral valve endocardium.
• Sudden death by prolapse into coronary ostia or occlusion of large coronary branch
Rhabdomyoma (most common tumor in children)
• Dependent on size, might result in cardiomegaly, congestive heart failure, and cardiac arrhythmias
• Sudden death or stillbirth
Fibroma (most common resected tumor in children)
• Approximately one third present with heart failure or cyanosis,
• One third with arrhythmias or syncope
• One third are asymptomatic and tumor discovery incidental
Atrioventricular nodal tumors
• Majority of patients present with complete heart block, the remainder experience sudden death
Cardiac lipomas
• Asymptomatic
• Rare extrinsic compression of heart dependent on size and location
Malignant tumors
Angiosarcoma
• Non-specific, depending on the location, right atrial lesions have propensity for pericardial involvement causing hemopericardium and pericardial constriction
• Chest pain, shortness of breath, malaise, and fever
Osteosarcoma
• Left atrial lesions present with respiratory symptoms
• Ventricular lesions present with recurrent ventricular tachyarrhythmia
Leiomyosarcoma
• Left atrial lesions (75%) present with pulmonary symptoms of dyspnea, chest pain, and non-productive cough
• Ventricular lesions may present with right heart failure, valve stenosis, rhythm alterations, conduction abnormalities, hemopericardium, and sudden death
Rhabdomyosarcoma
• Non-specific symptoms, sometimes pleuropericardial symptoms and distal embolization
• Arrhythmias and obstructive symptoms
Cardiac lymphoma
• Heart failure exertional dyspnea, atrial fibrillation, and features of right-sided heart obstruction
• Cardiac tamponade
Pericardial mesothelioma
• Chest pain, cough, dyspnea, and palpitations
Metastatic cardiac tumor (depends on the primary tumor as well as myocardial or pericardial involvement)
• Tachycardia, arrhythmias, cardiomegaly or heart failure in patients with carcinoma should raise suspicion of cardiac metastasis
• Rarely, cardiac involvement such as pericardial effusion or incipient cardiac tamponade can be first clinical feature of malignant disease, although 90% are clinically silent

Modified from Butany J, Nair V, Naseemuddin A, et al.: Cardiac tumours: diagnosis and management. Lancet Oncol 2005;6:219–28

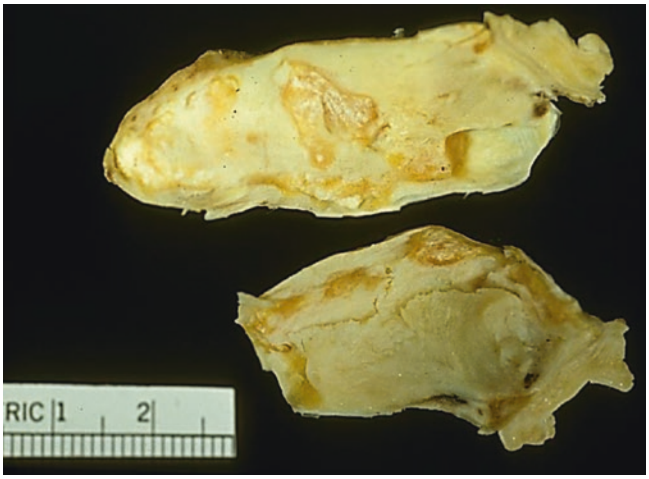

Fig. 74.1 Calcified mural thrombus (pseudotumor). This right atrial mass was removed from a patient with antiphospholipid syndrome. There was dense calcification resulting in rock-hard tumor that could be sectioned only after days of decalcification. The cut section is yellow-tan

Calcifying Amorphous Pseudotumor

Calcification within a mural thrombus often leads to the erroneous clinical diagnosis of cardiac myxoma [8, 9] (Fig. 74.1). Calcified mural thrombi may occur in any cardiac chamber, most commonly the right atrium, and are often associated with antiphospholipid syndrome or renal failure [10]. Histologically, there are abundant microcalcifications in a hyalinized stroma.

Mesothelial Pseudotumors

These are not true tumors and are incidental findings at surgery. Histologically, they are composed of macrophages, mesothelial cells, and fat globules removed from the heart and pericardium (Fig. 74.2). These structures lack stroma or vascularity. Originally considered a form of hemangioma [11], they are currently designated mesothelial/monocytic incidental cardiac excrescences, or cardiac MICE [12].

Ectopias

Cystic Tumor of the Atrioventricular Node

Cystic tumor of the atrioventricular (AV) node is a rare primary cardiac tumor that can cause sudden death. It is located at the base of the atrial septum in the region of the AV node. The majority of patients have congenital heart block, and almost three out of four are female. Most tumors occur sporadically, but there is an association with cysts of endocrine organs and other midline defects, such as ventricular septal defect, nasal septal defect, encephalocele, thyroglossal duct cysts, and absent septum pellucidum.

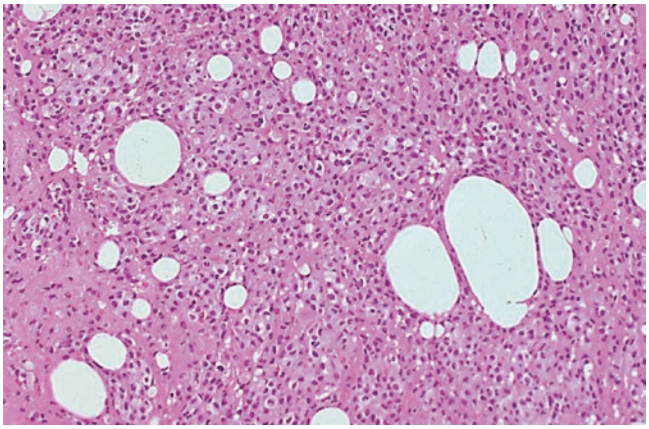

Fig. 74.2 Mesothelial/monocytic incidental cardiac excrescence. There is a collection of mononuclear cells and fat globules resembling a cytologic preparation. Note absence of stroma (H&E stain)

Histologically, there are multiple cysts in the area of the AV node and the nearby atrial tissues, without involvement of the central fibrous body or penetrating bundle. The cysts are lined by cuboidal, transitional, or squamous epithelium, and there is often a combination of epithelial elements. Many cysts are collapsed, forming nests of cells with an infiltrative appearance. There are no mitotic figures, or atypical features of the nuclei. Immunohistochemically, the lining cells are positive for cytokeratin, carcinoembryonic antigen, B72.3 antigen, and occasionally chromogranin [13–17].

Germ Cell Tumors of the Heart

Almost all germ cell tumors of the heart are teratomas, but rare yolk sac tumors have also been described within the pericardium [18–21]. The majority of cardiac teratomas are located in the pericardial sac in fetuses, newborns, infants or children. Rarely, they may occur within the myocardium in the ventricular septum or in the area of the AV node. Histologically, they resemble testicular teratomas, and are usually benign.

Benign Neoplasms

Papillary Fibroelastoma

An unusual lesion occurring exclusively on the endocardial surface, most commonly on valve leaflets, with the majority presenting as incidental findings at autopsy. It is a rare lesion with an estimated frequency of 0.0017–0.33% in autopsy

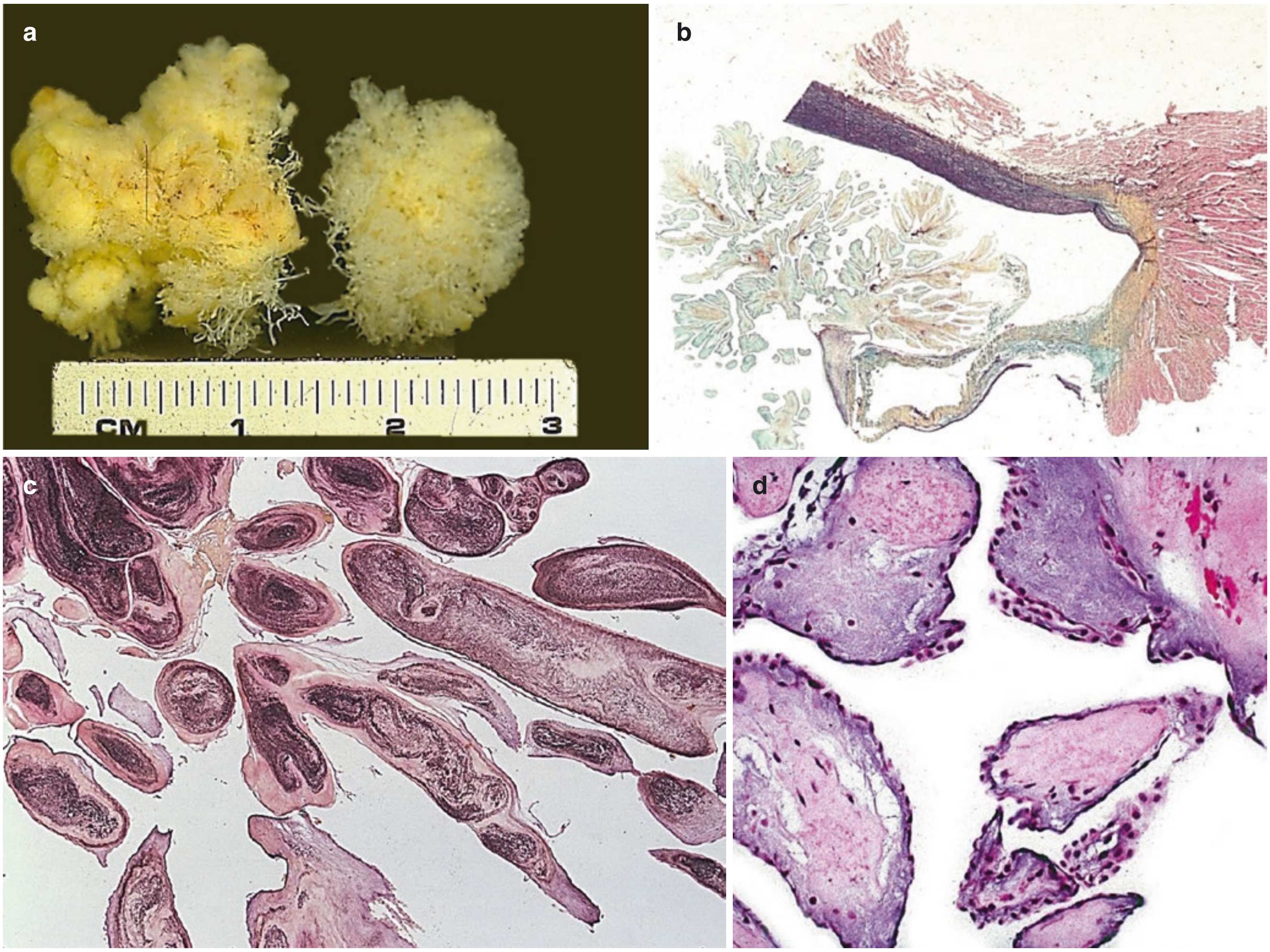

Fig. 74.3 Papillary fibroelastoma. (**a**) Shows typical gross appearance when placed in water. (**b**) Movat stained section shows aortic valve cusp with attached central stalk and papillary fronds characteristic of papillary fibroelastoma. (Reproduced with permission from Burke A. and Virmani R. Atlas of Tumor Pathology. Tumors of the Heart and Great Vessels). Higher magnification in (**c**) and (**d**) shows avascular papillary fronds lined by endothelial cells with interspersed mesenchymal cells in the core

series [22]. A papillary fibroelastoma is probably an exaggerated form of Lambl's excrescence [23], which is a reactive filiform growth that occurs at the sites of greatest hemodynamic stress, usually at the nodules of Aranti of the semilunar valves. They occasionally occur in areas of previous endocardial damage or in patients with preexisting heart disease. We have seen them in patients with prosthetic heart valves and previous radiation therapy. Unlike Lambl's excrescences, papillary fibroelastomas can become quite large, and occur on any valve surface or area of the endocardium.

Grossly, the papillary fibroelastoma looks like a "sea anemone" (Fig. 74.3a). Their most common location is the aortic valve, followed by the mitral and tricuspid valves, pulmonary valve, and endocardial surfaces. Histologically, they are avascular papillary structures lined by endothelial cells (Fig. 74.3b–d). The cells covering the surface express vimentin, factor VIII-related antigen, and CD34, and the stroma is rich in collagen type IV [24].

The major differential diagnosis is cardiac myxoma.

Rhabdomyoma

Rhabdomyoma is the most common primary cardiac neoplasm in children and it is intimately associated with the tuberous sclerosis syndrome. Patients with tuberous sclerosis will demonstrate multiple cardiac masses echocardiography, presumed to be rhabdomyomas, in infancy [25]. Conversely, 50% of patients with rhabdomyomas will have other manifestations of the syndrome, such as intracranial hamartomas, facial angiofibromas, subungual fibromas, linear epidermal nevi, renal angiomyolipomas, and other hamartomas [26, 27].

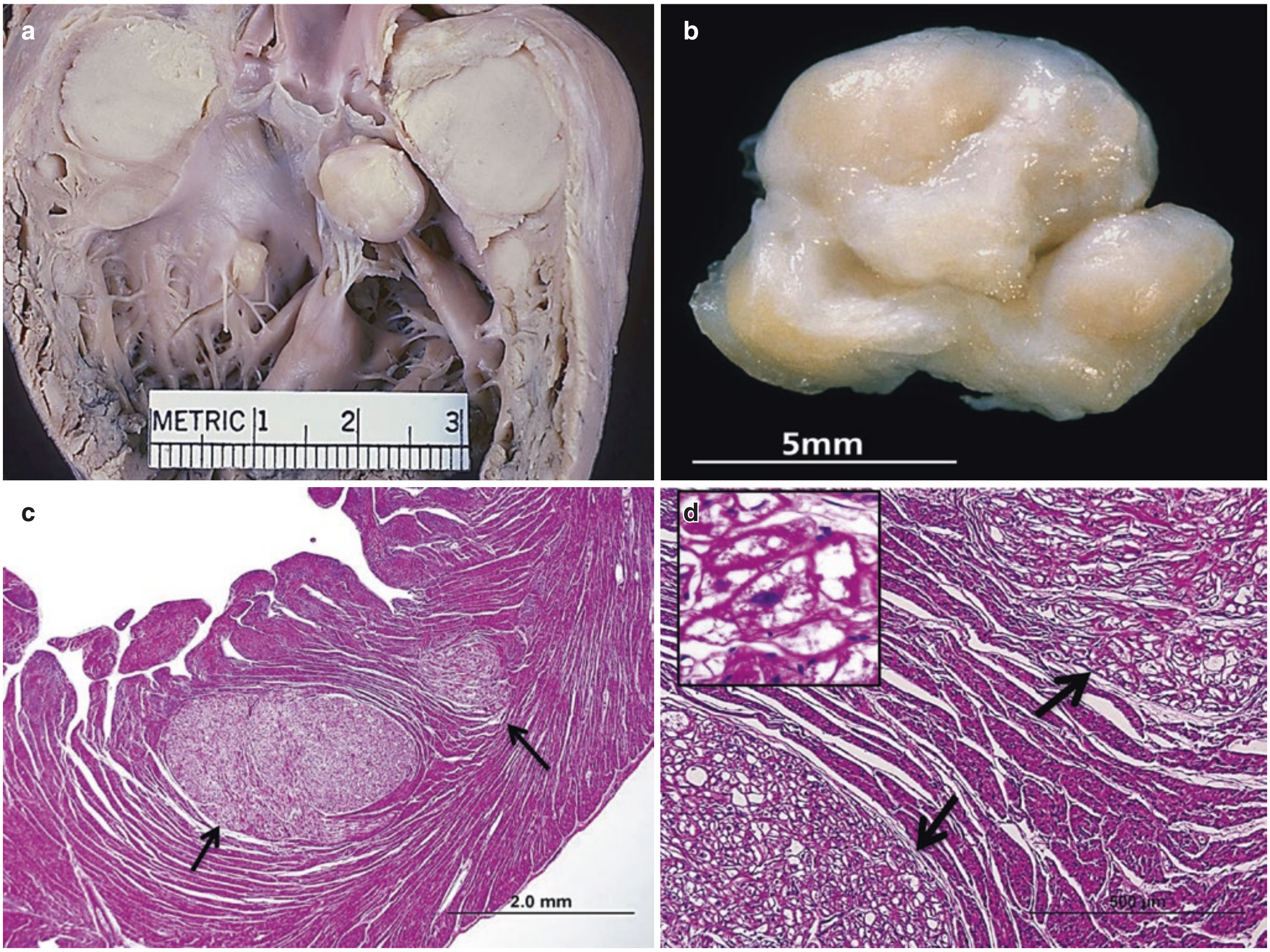

Fig. 74.4 Rhabdomyoma. (**a**) Apical four chamber view, showing multiple cardiac rhabdomyomas involving the left and right ventricles. Multiple rhabdomyomas in an infant with tuberous sclerosis complex (Courtesy of William D. Edwards, M.D.). (**b**) Subaortic rhabdomyoma in a 5-month-old child. (**c**, **d**) Histologic section shows two subendocardial rhabdomyomas (arrows) inset shows "spider" cells, several vacuolated tumor cells and cells with abundant eosinophilic cytoplasm

Rhabdomyomas in patients with tuberous sclerosis are usually multiple masses that with extensive cardiac involvement may result in intrauterine hydrops (Fig. 74.4a) [27, 28]. Sporadic rhabdomyomas are more likely solitary endocardial-based lesions that may cause ventricular outflow tract obstruction requiring surgical excision, or induce cardiac arrhythmias.

Cardiac rhabdomyomas are mostly diagnosed in the first few months of life, and the mean age at diagnosis is 2 months. It may also be detected in children and teenagers, and should, prompt the cardiologist to search for other manifestations of tuberous sclerosis [29].

Grossly, rhabdomyomas are well-demarcated yellow-tan nodules that occur within the myocardium or on the endocardial surface. Incidental rhabdomyomas are often endocardial lesions near the atrioventricular valves (Fig. 74.4b). The characteristic cell is the vacuolated "spider cell", which possess strands of cytoplasm emanating from the nucleus (Fig. 74.4c, d). The apparent spaces within the cell contain large amounts of glycogen. Ultrastructurally, there are glycogen granules, myofibers, dispersed Z-band material, and intercalated disks along the cell periphery [26].

There are few entities in the differential diagnosis. Vacuolated cells may occur in storage diseases in a diffuse, non-discrete, distribution. Purkinje cell hamartomas are usually smaller lesions with abundant mitochondria [30, 31].

Adult Cellular Rhabdomyoma

Adult cellular rhabdomyoma is a rare tumor that is histologically and clinically distinct from congenital rhabdomyoma. These tumors are considered to be true neoplasms with striated muscle differentiation, expansile growth, and evidence of cell proliferation. All have occurred in adults (34–55 years of age) and most are found in the atria [30, 31]. Electrical disturbances such as supraventricular tachycardia or nonsustained ventricular tachycardia are common.

Unlike congenital rhabdomyoma, vacuolated spider cells rarely present. The differential diagnosis includes rhabomyosarcoma but the absence of tumor necrosis, mitotic figures and the presence of a well-defined pseudo-capsule helps to distinguish it from the malignant rhabdomyosarcoma.

Lipomatous Hypertrophy of the Atrial Septum

Lipomatous hypertrophy of the atrial septum is a non nonencapsulated proliferation of mature fat, multivacuolated fat, and atypical cardiac myocytes occurring solely in the atrial septum resulting in a thickness greater than 2 cm [32–36]. In general, the fat deposit is measured above the oval fossa, where it forms a triangular mass roofed by the epicardial surface of the atria. Lipomatous hypertrophy occurs almost exclusively in adults, and there is an association with obesity [37, 38]. An association between interatrial fat deposits and arrhythmias, particularly atrial and supraventricular tachycardias, has been well established [34, 37, 39].

Recently, imaging techniques have allowed antemortem diagnosis [33, 38, 40]. The pre-operative diagnosis is usually right atrial myxoma, because the mass bulges into the right atrial cavity [38], or, if tissue density has been ascertained, the correct diagnosis is made before surgery [40].

Grossly, the tumor-like lesion is not encapsulated and bulges from the atrial septum. Histologically, there is a mixture of mature and brown fat, which ultrastructurally contains abundant mitochondria [38]. Entrapped, enlarged myocytes are common and may lead to the false diagnosis of sarcoma, or the brown fat clusters may be mistaken for lipoblasts.

Cardiac Lipoma

Encapsulated lipomatous neoplasms occur in the heart, but are very rare. Most are epicardial tumors, although any site of the heart may be affected (Table 74.4). Occasionally, they are multiple [41]. If small, they are usually an incidental finding at autopsy; larger lesions may result in pericardial constriction, heart failure, and sudden death.

Cardiac Fibroma

Cardiac fibroma is the second most common tumor of the heart in children after rhabdomyoma. Because of their intramural location, cardiac fibromas often cause cardiac arrhythmias. There is an association with the Gorlin-Goltz syndrome, or basal cell nevus syndrome [42], although most patients with cardiac fibroma do not have the full expression of that genetic disorder.

Grossly, a cardiac fibroma is a firm, white, bulging mass which appears circumscribed [43]. It may occur anywhere in the heart, but usually involves the ventricles with a predilection for the ventricular septum. The tumor may attain massive size in proportion to the heart itself (Fig. 74.5a) [44, 45]. Calcification is common, and it is a helpful feature distinguishing the tumor from a rhabdomyoma. Cardiac fibromas are virtually always single. Microscopically, it is characterized by fibroblasts in a collagenous background, with variable numbers of elastic fibers. Despite the gross impression, the borders of the lesion are infiltrating (Fig. 74.5b).

Table 74.4 Location of common cardiac neoplasms

Type of tumor	Left atrium	Right atrium	Left ventricle	Right ventricle	Valve	Pericardium
Myxoma	90%	10%	Rare	Rare	Rare	0
Sarcoma	46%[a]	26%	21% (right or left)[b]	[b]	0	7%
Fibroma	Rare	Rare	80% (majority in IVS)	20%	0	0
Papillary fibroelastoma	2%	[c]	10%	3% (right heart)[c]	85% (AV, MV)	0
Rhabdomyoma[d]	0	30% (atrium or ventricle)[e]	70% (and ventricular septum)	[e]	0	0
Lipoma (LI)/Lipomatous hypertrophy (LH)	0	Majority LH	Epicardial surface (LI)	Epicardial surface (LI)	0	0
Angioma	Any location	Any location	Any location	Any location	Varix	0

AV aortic valve, *MV* mitral valve, *IVS* interventricular septum

Modified from Burke A, Jeudy J, Jr., Virmani R: Cardiac tumours: an update. Heart 2008;94:117–123

[a] Angiosarcomas predominately arise in right atrium

[b] Right or Left

[c] Right heart

[d] 90% are multiple, and occur in newborn or children, rare in adults

[e] Atrium or ventricle

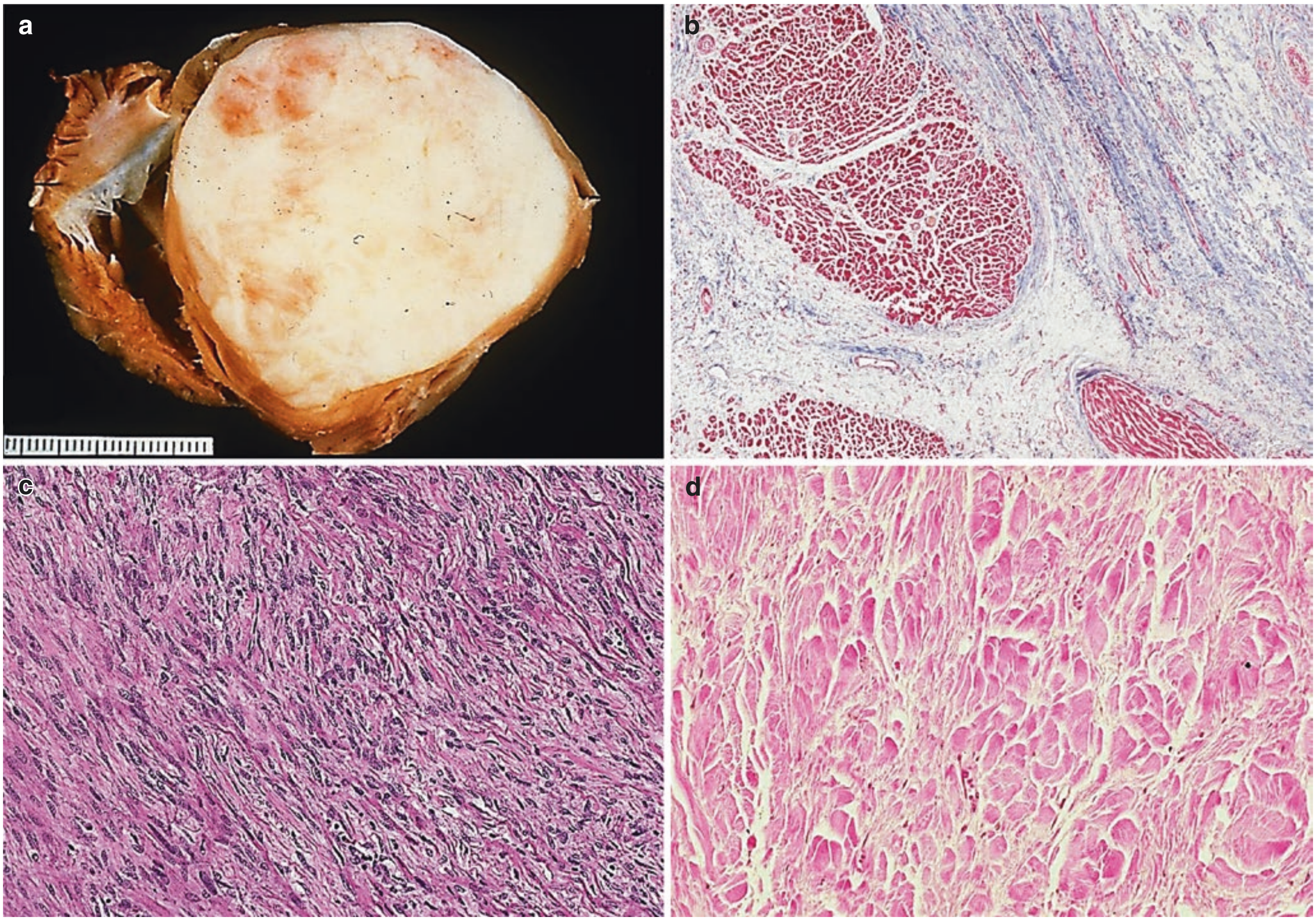

Fig. 74.5 Cardiac fibroma. (**a**) The tumor is a bulging firm white mass that often distorts the surrounding myocardium. This tumor obliterated the left ventricle and ventricular septum; note the tricuspid valve between the right atrium and the ventricle. (**b**) A trichrome stain demonstrates infiltration of the collagenous tumor into cardiac muscle (Masson-trichrome). (**c**) In children, cardiac fibromas may be markedly cellular, similar in appearance to fibrosarcoma. (**d**) In adults, the tumors are composed almost entirely of nearly acellular collagen (**c**, **d**, H&E stain)

Cardiac Myxoma

Cardiac myxoma is a distinctive neoplasm that arises exclusively in the cardiac endocardium, most commonly in the left atrium in the region of the interatrial septum and the fossa ovalis [46–50]. Cardiac myxomas are composed of a variety of cellular elements, including stromal and inflammatory cells that secrete interleukins and coagulation factors [51, 52]. The molecular basis of cardiac myxomas has recently been investigated highlighting specific protein markers responsible for sporadic and familial forms of cardiac myxomas [53].

Patients are, on average, 50 years of age at the time of diagnosis (Table 74.5), and there is a slight female predominance. Embolic phenomenon may cause cerebral ischemia, vision disorders following embolization to retinal arteries, claudication of the extremities, renal failure, coronary obstruction and sudden death [54]. A high proportion of tumors are found incidentally, representing approximately 15% of cases (Table 74.6). Constitutional symptoms are varied and are believed to be secondary to elaboration of interleukin-1, a polyfunctional cytokine which stimulates B-cell differentiation in plasma cells and may result in polyclonal hypergammaglobulinemia [55, 56].

Table 74.5 Sites of endocardial attachment and mean age in cardiac myxoma[a]

Site	Percent total	Mean age (years)
Single atrial tumors	89%	53 ± 17
Left atrium at interatrial septum	64%	
Right atrium at interatrial septum	15%	
Left atrium at other sites[b]	5%	
Right atrium at other sites	5%	
Multiple or ventricular tumors	11%	30 ± 11[c]
Multiple sites, right atrium	2%	
Multiple sites, left atrium	2%	
Multiple chambers	5%	
Left ventricle	1%	
Right ventricle	1%	

[a] Data derived from 128 cardiac myxomas (surgical and autopsy materials) reviewed by the authors

[b] Some of these cases involved the mitral valve annulus or leaflets

[c] Difference significant, $p < 0.0001$

Table 74.6 Initial symptoms in cardiac myxoma[a]

	N		
Symptom or initial manifestation	Left-sided	Right-sided	Total
Embolism	24	2	26
To central nervous system	18	–	18
To lower extremities	5	–	5
To kidneys (hematuria)	1	–	1
Lungs (pulmonary embolism)	–	2	2
Pulmonary congestion/heart failure	20	3	23
Shortness of breath/orthopnea	11	0	11
Dyspnea on exertion	7	1	8
Ankle edema	0	2	2
Hemoptysis	2	0	2
Arrhythmia/syncope	15	5	20
Syncope	3	3	6
Sudden death	5	0	5
Palpitation	3	0	3
Supraventricular tachycardia	3	0	3
Atrial fibrillation/flutter	1	1	2
Sick sinus syndrome	0	1	1
Incidental finding/no symptom	7	8	15
Detected at auscultation	4	5	9
Detected at chest X-ray	2	3	5
Detected at angiography for ischemic heart disease	1	0	1
Constitutional symptoms	0	6	6
Weakness	0	2	2
Fatigue	0	2	2
Weight loss	0	1	1
Fever of unknown origin	0	1	1
Other	7	3	10
Chest pain	5	1	6
Found in evaluation for syndrome	1	1	2
Fever/bacterial endocarditis	1	1	2
Total	73	27	100

[a]Data derived from 100 cardiac myxomas reviewed by the authors, excluding incidental myxomas found at autopsy

The diagnosis of a cardiac myxoma is generally made at echocardiography (Fig. 74.6a–d). Angiography is performed in elderly patients to evaluate the coronary arteries, and often demonstrates a moderate degree of pulmonary hypertension in individuals with left atrial tumors. Transesophageal echocardiography, computed tomography, and magnetic resonance imaging may be superior to transthoracic echocardiography in demonstrating precise tumor attachment and differentiating the lesion from a mural thrombus or atrial sarcoma. Over three-fourths of tumors are located in the left atrium, and the majority of the remainder arises in the right atrium. Multiple tumors and tumors located in sites other than the fossa ovalis are rare, and occur more frequently in patients with myxoma syndrome.

Surgically, tumors with a narrow stalk may be resected without removing atrial septal tissue. In many patients, however, a portion of atrial septum including the fossa is excised and a synthetic or pericardial patch is placed in the defect. If the site of attachment is multifocal or is located in the atrial free wall, myxoma syndrome should be suspected, or the lesion is likely a myxoid sarcoma. The post-operative prognosis of cardiac myxoma is excellent. The recurrence rate in combined series is less than 2% [57%].

Cardiac myxoma are heterogeneous, variegated tumors with approximately two-thirds represented as round to oval sessile polypoid masses with a short broad base attached to the atrial septum and smooth or slightly bosselated surface. The remaining one-third are soft and gelatinous with an irregular surface consisting of papillary or finger-like villi that are prone to embolization [50]. Calcification is common. Irregular tumors are more likely gelatinous and myxoid and are prone to embolization, in contrast to smooth-surfaced lesions, which often contain abundant collagen and are unlikely to fragment and dislodge into the circulation. Cardiac myxomas arising on cardiac valves are distinctly rare.

The cardiac myxoma arises from the endocardium, usually in the region of the fossa ovalis. The histologic diagnosis of cardiac myxoma depends on the identification of the myxoma cell, which is a polygonal (lepidic) or stellate syncytial cell. Towards the surface of the tumor, myxoma cells are closely associated with capillaries, often forming rings. The myxoid stroma contains dendritic cells that express factor XIII, KP-1 positive macrophages, many of which contain hemosiderin, and scattered lymphocytes. In over one-half of tumors, there is extensive scarring replacing the myxoid areas, and calcification and metaplastic bone may be present in right atrial myxomas. Hemorrhage and organizing thrombus result in abundant hemosiderin-laden macrophages, which are virtually always present and is a helpful diagnostic feature. In 10% of tumors, elastic tissue and calcification surround the hemosiderin, resulting in Gamna–Gandy bodies. Invasion of the tumor into the myocardium is not a feature of cardiac myxoma and mitotic figures are rare.

The myxoma cell is variably positive for S-100 protein, Notch1, calretinin, caldesmon, tenascin C, alpha smooth muscle actin (α-SMA), CD31, vimentin [57] and occasionally positive for MMP1, MMP2, and TIMP-1 [58]. A variety of other antigens have been demonstrated in the myxoma cell, including S-100, cytokeratin, desmin, myoglobin, Ulex europaeus lectin α binding (focally), factor VIII-related antigen and CD34 [24, 59–61]. The dendritic cells express factor XIII [52], and the endothelial cells CD34 and factor VIII related antigen.

Approximately 5–10% of patients with cardiac myxoma shows a familial inheritance and occur as part of the Carney complex (CNC). The Carney complex, first described in 1985 is an X-linked autosomal dominant syndrome characterized by lentigines, blue nevi, extracardiac myxomas (mucosal and cutaneous), Schwannomas, endocrine overactivity, calcifying Sertoli cell tumors of the testis, and other lesions [62–67]. In the myxoma syndrome, myxomas are

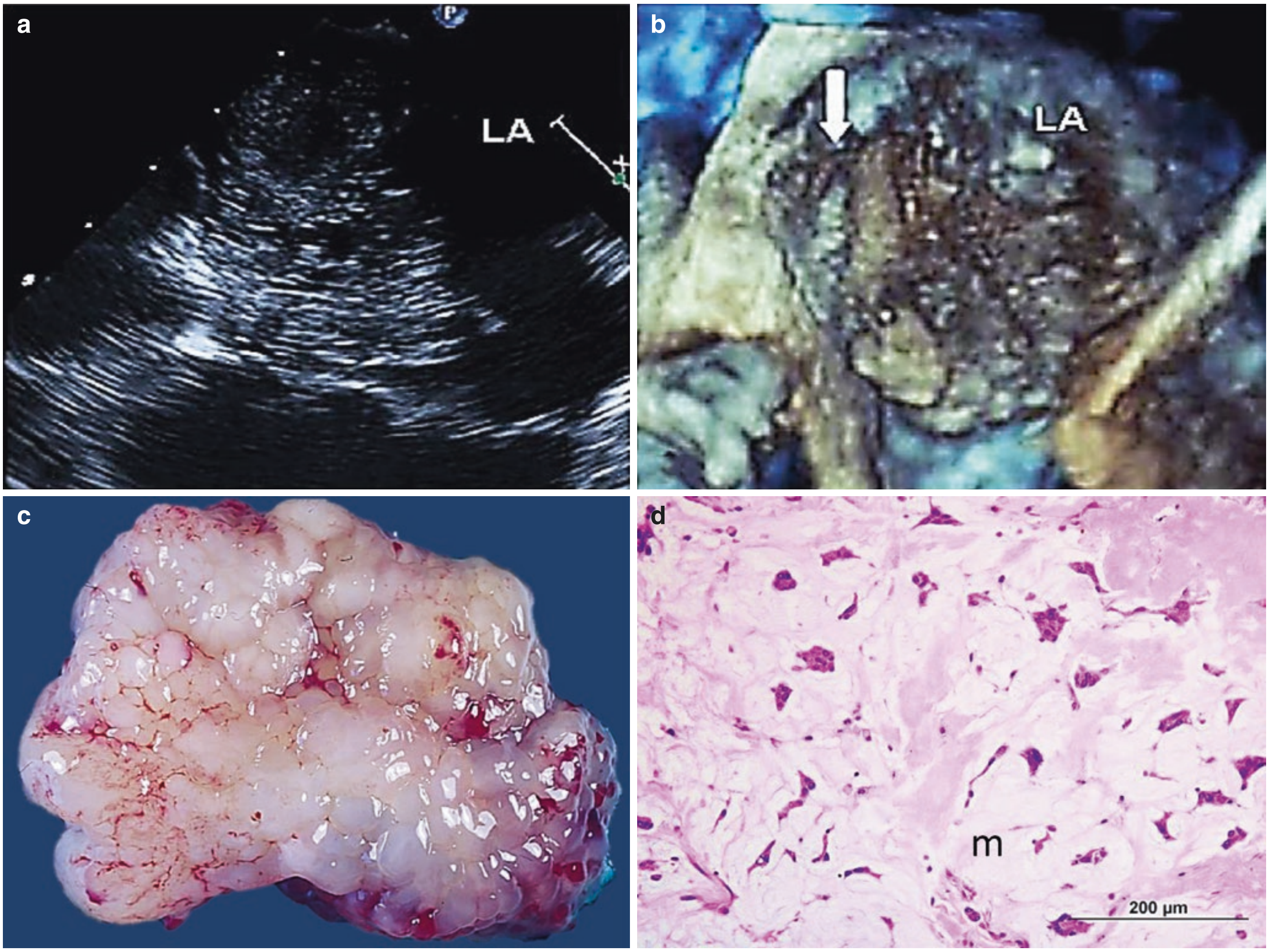

Fig. 74.6 Cardiac myxoma. (**a**) Two-dimensional transesophageal echocardiographic image of left atrial myxoma showing multiple papillary excrescences but no distinct stalk. (**b**) Real-time 3D transesophageal echocardiographic surgical view of the mass through a left atrial cut shows a very friable tumor with multiple frond-like extensions. White arrow, dense stalk (*Reproduced with permission from Tolstrup K, et al. J Am Soc Echocardiogr 2011*). (**c**) Papillary myxoma after resection (*Reproduced with permission from: Tumors of the Lung, Pleura, Thymus and Heart. Eds. Travis WD, Brambilla E, Muller-Hermelink H-K, Harris CC. World Health Organization Classification of Tumor. WHO Press, Geneva, Switzerland. 2004. P 261*. Fig. 4.11E). (**d**) High-power microscopic image showing myxoid stroma (m) with lepidic cells arranged singly and in cords, typical of myxoma. *LA* left atrium

often multiple, show no female predilection, frequently recur or embolize, and do not necessarily occur at the fossa ovalis.

Various studies have identified 34 protein markers involved in the histogenesis and development of cardiac myxoma [68]. These demonstrate overlapping functions and overlapping signaling pathways such as G protein coupled receptors, TGF β receptor, VEGF receptor, MAP kinase, growth receptor signaling pathways, cytokine-cytokine receptor and intracellular signaling cascades [69]. Interestingly, papillary myxomas show increased expression of matrix metalloproteinases such as MMP-1, MMP-2, and MMP-9, which mediate degradation of extracellular matrix and may partially explain the tendency of these tumors to embolize [70]. Increased expression of MUC1, IL-6, and alpha1-globulin are also associated with increased risk of embolization [71].

Cytogenetic studies have detected two loci of susceptibility genes suspected to play a role in Carney complex, CNC 1 and CNC2 [72, 73]. The CNC1 susceptibility gene (PRKAR1A) is a tumor suppressor gene located at 17q22–24 and is found in the majority of familial CNC cases while the CNC2 gene is located on 2p16 without the PRKAR1A mutation [72, 74–76]. In contrast, no single gene mutation has been identified in the sporadic CNC. However structural rearrangement in PRKAR1A has been identified in one-third of cases of sporadic CNC [77].

The differential diagnosis of cardiac myxoma includes papillary fibroelastoma, primary or metastatic sarcomas and inflammatory myofibroblastic tumor, organizing thrombus and hemangioma (Table 74.7) [78, 79]. Sarcomas do not possess myxoma cell structures and abundant hemosiderin, and demonstrate mitotic figures and nuclear atypia (Table 74.8). Immunohistochemistry may help to differentiate myxoma from cardiac malignancies (Table 74.9).

Table 74.7 Differentiating features of cardiac myxoma and mural thrombus

	Mural thrombus	Myxoma
Gross		
Common attachment site	Atrial appendage Ventricular endocardium	Fossa ovalis, left side
Typical appearance of cut surface	Layered, with light and dark bands	Variegated, myxoid
Microscopic		
Cellular composition	Fibrin, red cells and leukocytes Endothelial cells Scattered fibroblasts Hemosiderin-laden macrophages (few)	Myxoma cells Hemosiderin-laden macrophages (numerous) Dendritic cells Capillaries
Immunohistochemical profile	Actin + fibroblasts Endothelial cells expressing endothelial markers	Cytokeratin negative S-100 variably positive CD 31 and 34 variably positive Factor VIII + dendritic cells Calretinin variably positive

Table 74.8 Differential features of cardiac myxoma and cardiac sarcoma

Feature	Myxoma	Sarcoma
Diagnostically helpful		
Myxoma cell rings, cords	++ to +++	0
Hemosiderin laden macrophages	++ to +++	0 to +
Factor XIII + dendritic cells	+ to +++	0
Mitotic figures	0 to +	+ to +++
Cellular atypia	0 to +	+ to +++
Compact spindle cells	0	+ to +++
Not diagnostically helpful		
Myxoid stroma	+ to +++	0 to +++
Fibrosis	+ to +++	+ to +++
Calcification	0 to ++	0 to +

Malignant Tumors

Primary Cardiac Sarcomas

Although rare, almost all cardiac malignancies are sarcomas and are classified similarly to sarcomas of extracardiac soft tissue. Cardiac sarcomas are generally of two basic histologic groups (1) angiosarcomas, which are generally found in the right atrium and (2) malignant fibrous histiocytoma/undifferentiated sarcomas, which typically arise in the left atrium [80, 81]. The majority of patients with primary cardiac sarcomas are adults. The mean age of about 40 years at presentation is slightly younger than that of cardiac myxoma (50 years) [82]. Sarcomas of the heart in children are quite rare. There is no sex predilection.

Angiosarcoma

If the subtypes of undifferentiated and myofibroblastic sarcomas are considered separately, angiosarcoma is the most common type of cardiac sarcoma [83], accounting for approximately 37% [3, 84–89]. The age range is 9–80 years, with a mean of 40 years [90]. Unlike other cardiac sarcomas, there is a marked right-sided predominance, nearly 90% occurring in the right atrium near the atrioventricular groove [3, 85–90]. Presenting clinical symptoms are most often related to hemopericardium or pericardial constriction, and are rarely caused by distant metastases [91]. Because of the propensity for pericardial involvement, cardiac tamponade occurs more frequently than with other types of cardiac sarcomas. Metastases occur in 66–89% of patients, most often to the lungs.

Cardiac angiosarcoma is typically a multicentric mass replacing the right atrial wall and either protruding into or filling the chamber. The size ranges from 2.0 to 17 cm in greatest dimension [92]. The mass or masses are typically dark red or brown (Fig. 74.7a). Invasion of the vena cava and tricuspid valve is common, but the atrial septum and pulmonary artery are usually spared. The pericardium is frequently involved, and may be the only site of the tumor.

Approximately two-thirds of primary cardiac angiosarcomas can be considered well to moderately differentiated and are characterized by well formed, anastomosing vascular

Table 74.9 Immunohistochemical profile of cardiac myxoma imitators

Tumor	CK	Vim	SMA	Desmin	Myo	S-100	CD31	CD34	FVIII
Inflammatory myofibroblastic tumor	F	+	+	F	–	–	–	–	–
Low grade fibromyxoid sarcoma	–	+	–	–	–	–	–	–	–
Myxoid Liposarcoma	–	–	–	–	–	+	–	–	–
Myxofibrosarcoma	–	+	F	–	–	–	–	–	–
Leiomyosarcoma	F	–	+	+	–	–	–	–	–
Angiosarcoma	F	–	–	–	–	–	+	+	+

CK cytokeratin, *VIM* Vimentin, *SMA* α smooth muscle actin, *Myo* myogenin, *FVIII* Factor VIII, *F* Focal, + positive, − negative
Modified from Singhal P, Luk A, Rao V, et al.: Molecular basis of cardiac myxomas. Int J Mol Sci 2014;15:1315–1337

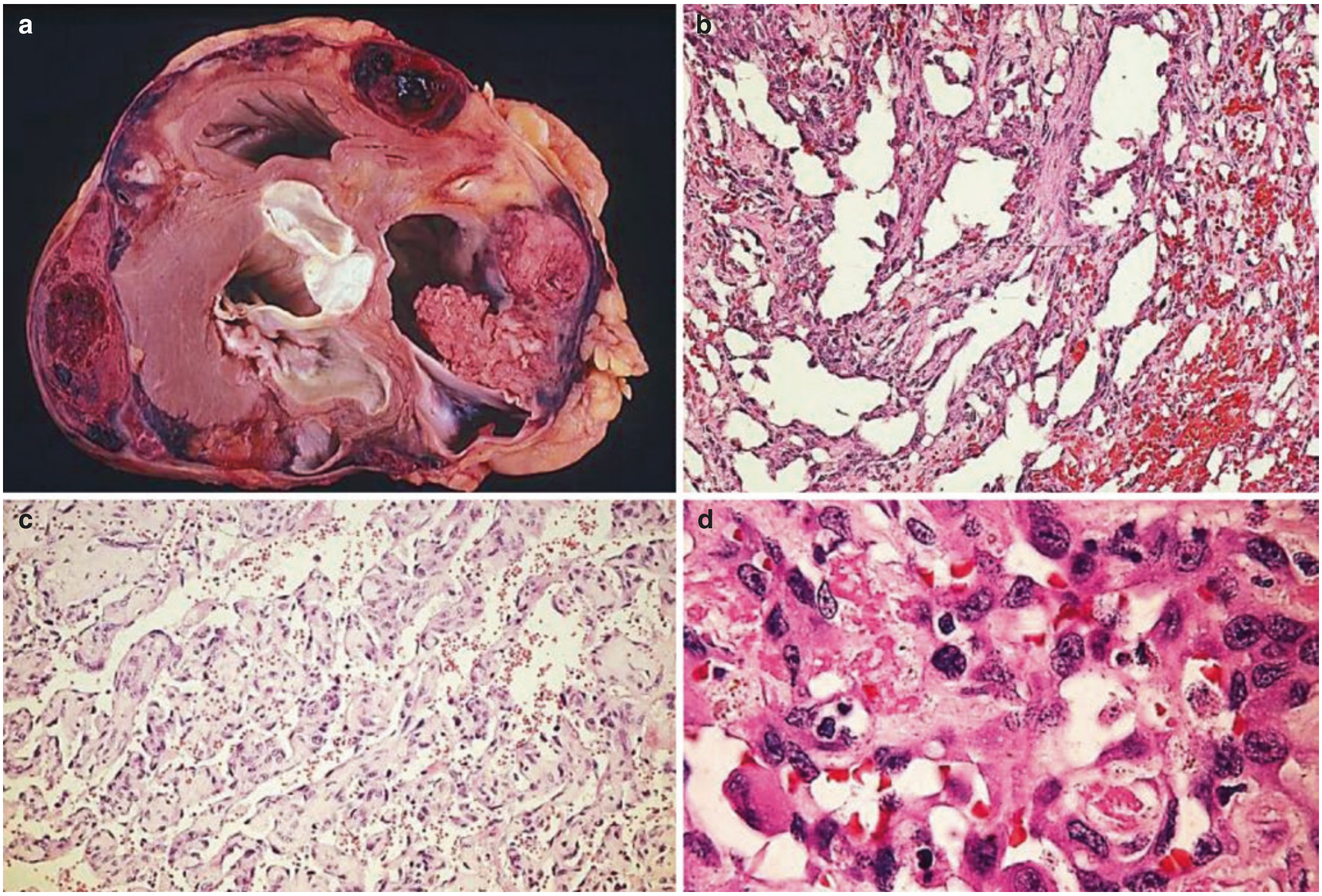

Fig. 74.7 Cardiac angiosarcoma. (**a**) Cardiac angiosarcoma arising in atrioventricular groove, forming a papillary mass. Note extensive pericardial involvement (Courtesy of Dr. William D. Edwards, M.D.) (*Reproduced with permission from Burke A, Tazelaar H, Veinot JP, Virmani R, Butany JW, Kamiya H, Loire R, Geva T, Watanabe G, Granmougin D, Bonilla F, Horimoto M, Galvin JR, Hiraga H. Cardiac Sarcomas. In: Travis W, Brambilla E, Muller-Hermelink HK, Harris C, eds. World Health Organization Classification of Tumours. Lyon: IARC Press, 2004. Figure 4.24 A and B*). (**b**) Histologically, irregular vascular channels are lined by typical endothelial cells. (**c**) Another typical pattern is that of anastomosing papillary structures lined by atypical endothelial cell. (**d**) The cells are large with with prominent eosinophilic cytoplasm with cytoplasmic vacuoles containing red cells. Nuclei are large and hyperchromatic and had prominent eosinophilic nucleoli

channels (Fig. 74.7b) or papillary structures (Fig. 74.7c) lined by pleomorphic malignant endothelial cells with varying amounts of atypia and mitoses (Fig. 74.7d) [92]. There may be areas of anaplastic or spindle cells with poorly formed vascular channels that resemble leiomyosarcoma or fibrosarcoma, but large numbers of extravascular erythrocytes and the identification of vacuoles with red blood cells may help in the diagnosis. Extensive sampling is important to detect endothelial vacuoles or diagnostic papillary structures in cardiac angiosarcomas with spindle cell areas.

Immunohistochemical studies indicate that factor VIII-related antigen, although a specific marker, is not particularly sensitive [93, 94]. Most angiosarcomas express endothelial markers such as CD31 and CD34 in the cells lining the vascular channels or papillary structures. In addition, laminin or type IV collagen can highlight vascular channels [95] and in areas of endothelial differentiation, cytokeratins can be diffusely positive [93]. Angiosarcomas of the pericardium can be quite difficult to diagnose in pericardial biopsies, and may be mistaken for mesothelioma or reactive mesothelial hyperplasia [96]. Nests of reactive mesothelial cells may become incorporated into the sarcoma and be mistaken for malignant cells. In these cases, immunohistochemical stains for cytokeratin and endothelial markers (factor VIII related antigen, CD31 and CD34) may help delineate the two populations of cells.

Epithelioid angiosarcomas have not been reported in the heart. However, epithelioid hemangioendothelioma, a related low grade tumor of vascular origin, may rarely arise in the atrium [97]. It is composed of round or oval epithelioid cells arranged in short strands or solid nests with intracellular lumens that may mimic the vacuoles of adenocarcinoma. Similar to anigosarcoma, immunohistochemical stains for factor VIII-related antigen, CD31 or CD34 help identify the cells [80].

Undifferentiated Pleomorphic Sarcomas (Malignant Fibrous Histiocytoma)

Sarcomas with variable degrees of myofibroblastic differentiation include a spectrum of high grade sarcomas that have been left unclassified or termed undifferentiated pleomorphic sarcoma (WHO designation) and malignant fibrous histiocytoma, now regarded as synonymous with undifferentiated pleomorphic sarcoma. The majority of these tumors arise in the left atrium, most commonly the posterior wall and less frequently the atrial septum. They are endocardial based and may be soft or firm polypoid lesions, sometimes distending the left atrium. They demonstrate fibroblastic or myofibroblastic differentiation with marked cellular pleomorphism and express intermediate filaments vimentin and smooth muscle cell actin [82, 93]. The mean age is approximately 45 years (range 20–80 years) with rare cases reported in infants [80]. The term "intimal" sarcoma is sometimes used for these lesions as sarcomas of similar morphology arise in the pulmonary artery and aorta [98–102]. Use of the term "intimal" sarcoma has recently been the subject of debate as a true intimal layer as seen in the vasculature is not present in the endocardium lining the heart [81].

The most common clinical symptom is dyspnea related to obstruction of the mitral valve [103], because they most often occur in the left atrium. Other symptoms may occur including malaise, fever, chest pain, weight loss, palpitations, syncope, and stroke [82]. The most common clinical diagnosis is a cardiac myxoma. Imaging studies may demonstrate multiple attachment sites, mitral valve involvement, or infiltration into atrial or ventricular walls, none of which occur with cardiac myxoma. Occasionally, complete tumor resection is impossible, and a palliative procedure is performed.

Like all cardiac sarcomas, the prognosis for myofibroblastic cardiac sarcoma is poor, generally measured in months [3, 82, 85–89]. There is no evidence that one histologic type imparts a worse prognosis than any other [86]. It has been shown that high-grade tumors, those with numerous mitoses or necrosis, are more clinically aggressive than those with few mitoses and no necrosis. The most important factor affecting the prognosis of these tumors is the anatomical location in the heart (intracavitary versus intra/extramyocardial growth).

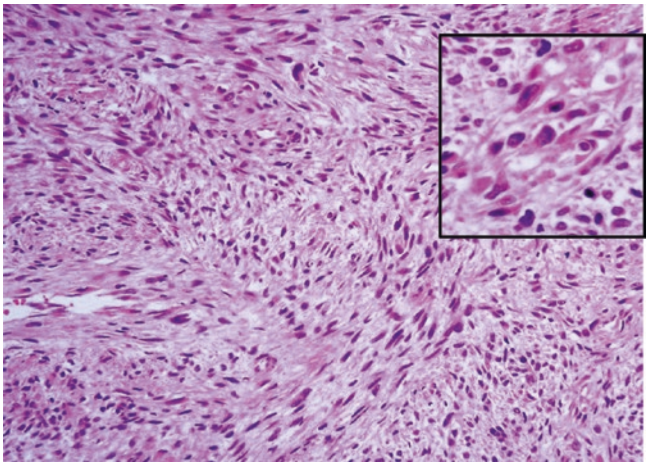

Fig. 74.8 Malignant fibrous histiocytoma. Histologic appearance is variable, but this tumor showed spindle cells arranged in a storiform pattern with marked pleomorphism and fibrohistiocytic appearance. Mitotic figures were easy to find. Insert shows pleomorphic nature of the tumor

The histologic features of these cardiac sarcomas are identical to their extracardiac counterparts. In general, malignant fibrous histiocytoma is a poorly differentiated mesenchymal malignant tumor of fibroblastic or myofibroblastic differentiation, consisting of atypical spindle cells with variable degrees of atypia, mitotic activity, necrosis, nuclear polymorphism (Fig. 74.8), and often demonstrates prominent vascularity. A large proportion of malignant fibrous histiocytomas and fibrosarcomas of the heart demonstrate extensive myxoid changes in the stroma perhaps because of their luminal location [104–107]. The term "myxosarcoma" is often used in the surgical literature for these tumors, although it is probably best to avoid this designation, as it may give the erroneous impression that the tumor arose from a benign myxoma. In fact, there is very little evidence that cardiac myxomas undergo progressive malignant "transformation".

These sarcomas usually show positive immunoreactivity for vimentin, osteopontin, and MDM2 [108, 109]. Variable positivity for alpha smooth muscle actin, CD117, CD68, p53, and bcl2 has also been reported. Occasionally, the tumor has some positive staining with antibodies against desmin. Factor VIII, CD31 and CD34 are typically negative, but may be positive in areas with angiosarcomatous differentiation, indicating the undifferentiated mesenchymal origin of the tumor, with occasional tendency towards differentiation to a specific type of connective tissue.

The primary differential diagnosis for myofibroblastic sarcomas is a cardiac myxoma. In general, the distinction is easily made, provided that myxoma cells, hemosiderin laden macrophages, and factor XIII positive dendritic cells are absent.

Leiomyosarcoma

Approximately 10% of cardiac sarcomas demonstrate smooth muscle cell differentiation [110–113]. Leiomyosarcomas are composed of fascicles of spindle cells that intersect with one another at right angles. Intracellular glycogen is present and over 50% of tumors show focal desmin expression.

The mean age of patients with cardiac leiomyosarcoma is 30 years, approximately 15 years younger than most other cardiac sarcomas. Like myofibroblastic sarcomas, most

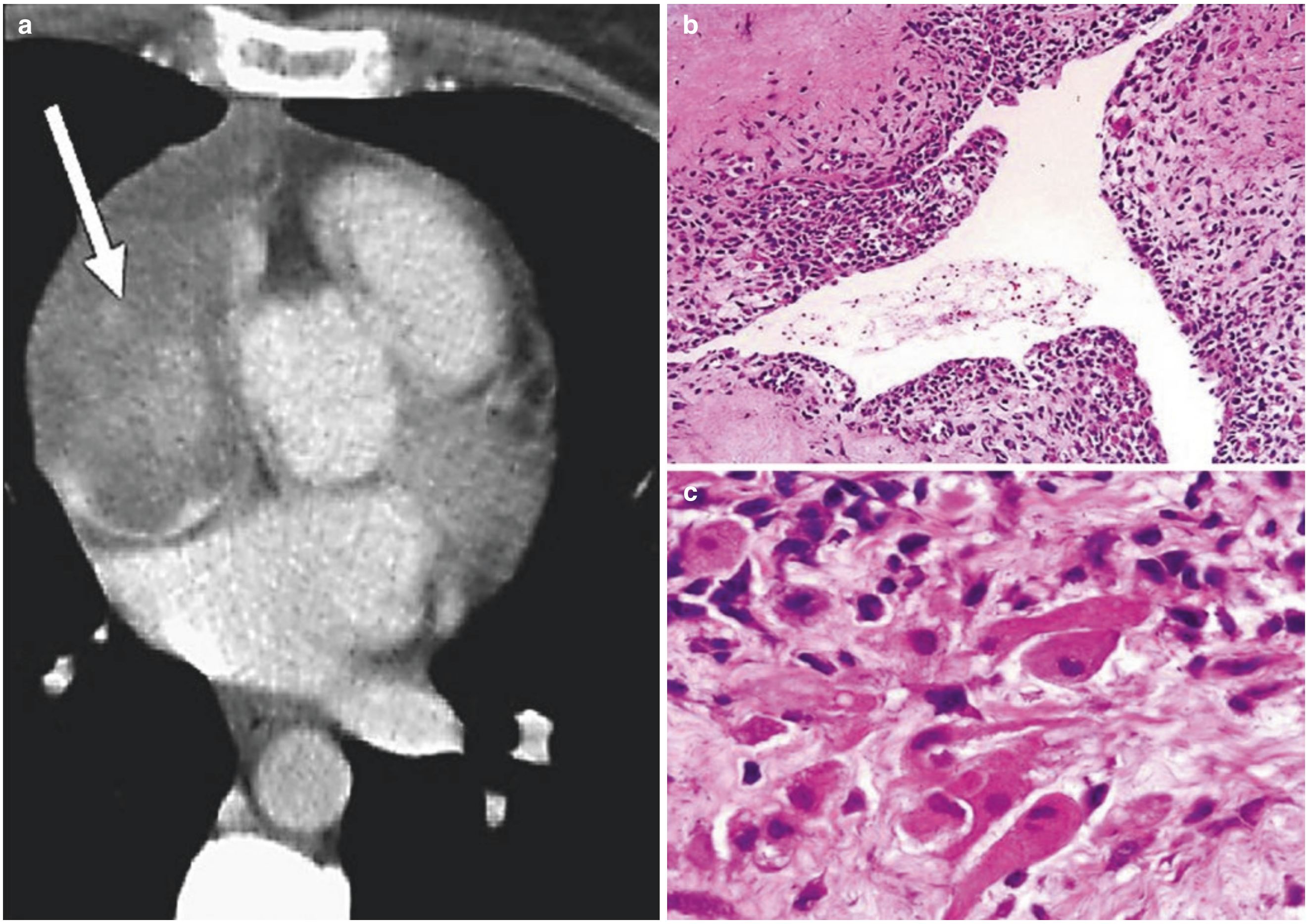

Fig. 74.9 Rhabdomyosarcoma. (**a**) Single-detector single-source CT of the chest with intravenous contrast performed in a 42-year-old woman. CT imaging demonstrates an irregular mass starting at the confluence of the superior vena cava and right atrium extending to completely involve the right atrium (arrow) (*Reproduced with permission from Anavekar NS et al. Computed tomography of cardiac pseudotumors and neoplasms. Radiology Clin N Am 2010;48:799–816; Figure 25*). (**b**) Embryonal rhabdomyosarcoma masquerading as a small cell undifferentiated tumor with cellular areas concentrated towards the surface, which has also been observed in myxomas. (**c**) Rhabdomyoblasts, some tadpole shaped with large eosinophilic cytoplasm

tumors arise in the left atrium. A certain proportion of atrial leiomyosarcomas may derive from veins emptying the heart [114], either the venae cavae on the right or pulmonary veins on the left side.

Rhabdomyosarcoma

Rhabdomyosarcomas constitute approximately 5% of cardiac sarcomas [82, 86, 88, 89, 93]. Unlike cardiac sarcomas with fibrous or smooth muscle differentiation, cardiac rhabdomyosarcoma does not show any predilection for the left atrium; either atrium or ventricle may be the primary site. Cardiac rhabdomyosarcoma is slightly more common in males than females, at a ratio of 1.4:1 [115]. The mean age at presentation is younger than that of other cardiac sarcomas, in the second to third decade. These are bulky, invasive tumors that may exceed 10 cm in the greatest diameter. The majority are of the embryonal type and may be well differentiated with numerous tadpole-shaped rhabdomyoblasts (Fig. 74.9a–c). Round cell tumors, by contrast, may show very few rhabdomyoblasts, which are identified only after extensive search. Rhabdomyoblasts contain abundant glycogen, and express desmin and myoglobin, helpful immunohistochemical markers. The alveolar subtype of embryonal rhabdomyosarcoma has been described in the heart as a metastatic lesion [116], and cardiac sarcoma botryoides, another form of embryonal rhabdomyosarcoma, has also been reported [117].

Cardiac Lymphoma

Primary cardiac lymphomas (PCL) that present with cardiac symptoms and are largely intrapericardial, are rare, and generally diagnosed at autopsy [118–121]. They account for 1.3% of primary cardiac tumors and 0.5% of extra nodal lymphomas with a male predominance (male to female ratio 3:1).

Although there are occasional reports of cardiac lymphomas diagnosed at surgery [119, 122], many series of surgically excised cardiac tumors do not include examples of lymphoma [3, 86, 87, 89, 93]. At the time of the last Fascicle on Cardiac Tumors from the Armed Forces Institute of Pathology in 1996 a total of 38 primary lymphomas had been published, since then another 50 or so have been added. The largest series of five cases comes from Brigham and Women's Hospital with three patients presenting with chest pain and three had dyspnea. One patient had bradycardia but none had constitutional symptoms [123].

Some believe that the incidence of PCL is increasing due to Epstein-Barr related lymphoproliferative disorders in AIDS [124] and post-transplant patients [125, 126]; others claim this increase is secondary only to advances in the diagnostic capability of imaging techniques. Post-transplant lymphoproliferative disease may develop within months or many years after transplant [127]. The incidence of post-transplant lymphomas, at any site, is greater in patients with heart and lung transplants, approximately 6%, than those with renal transplants, less than 1% [128]. However, PCL comprise less than 5% of all lymphomas arising in patients with AIDS and organ transplants [128–130], and location of the tumor in the donor heart is the exception rather than the rule in heart transplant patients [126]. Therefore, despite the increased prevalence of Epstein-Barr related lymphomas, a considerable proportion of PCL still occur in immunocompetent patients. There is no evidence that cardiac lymphomas arising in immunocompetent patients contain genomic Epstein-Barr virus DNA [120].

Patients with cardiac lymphomas may complain of a variety of symptoms, including cardiac tamponade [131], heart failure [121, 124, 126], exertional dyspnea, atrial fibrillation or flutter [132, 133], and right heart obstruction [119, 134]. In general, poor outcomes have been reported following diagnosis with the majority of patients dying within several months of diagnosis [135].

Grossly, any portion of the heart may be involved by lymphoma, although there is a slight predilection for the right atrium [118, 123]. Generally, the heart demonstrates multiple firm whitish-yellow nodules. They rarely show necrosis or valvular involvement unlike the more common malignant sarcomas.

Histologically, cardiac lymphomas span the spectrum of B cell proliferations, and include follicle center cell lymphomas, immunoblastic lymphomas, diffuse large cell lymphomas, Burkitt lymphoma and rare cases of T-cell lymphoma, small lymphocytic lymphoma, and plasmacytic lymphoma (Fig. 74.10a–d) [135, 136]. Immunocytochemical staining, cytogenetics, and polymerase chain reaction have been performed to confirm the lymphoid lineage and detect the presence of a monoclonal population [137, 138]. Diffuse large B cell lymphoma is the subtype most frequently observed (80% of published cases).

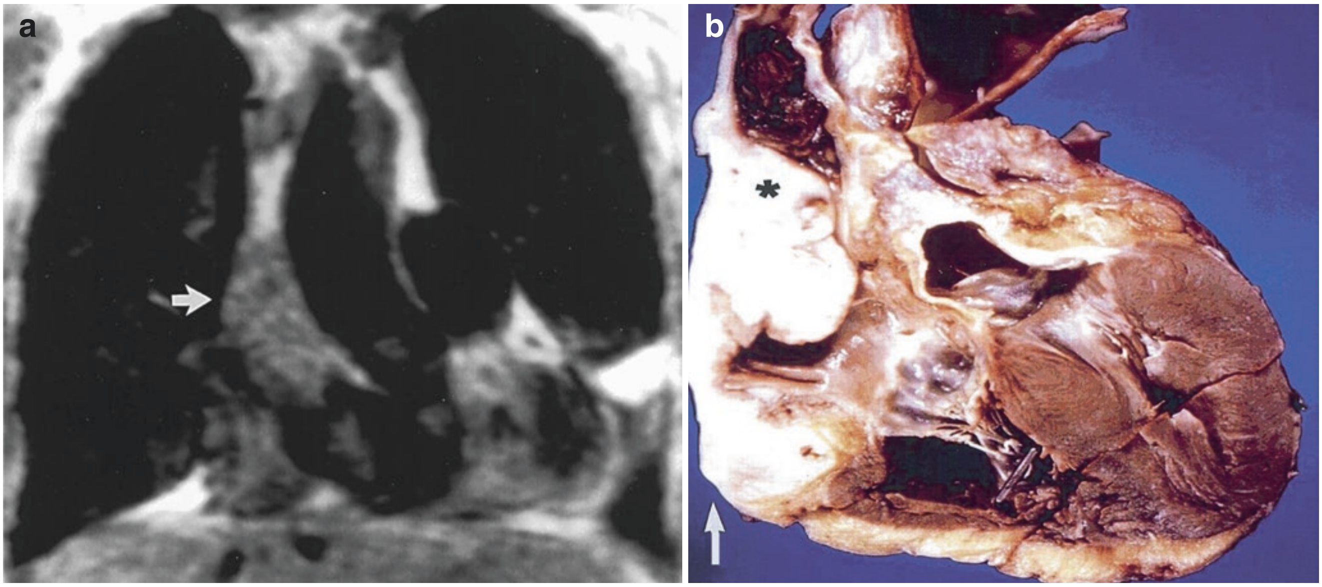

Fig. 74.10 Primary cardiac lymphoma. Primary cardiac lymphoma in a 75-year old woman with progressive dyspnea, superior vena cava syndrome and atrial fibrillation. (**a**) Coronal T1-weighted MR image shows vena cava invasion (arrow) by a mass. (**b**) Photomicrograph of the specimen of the heart obtained at autopsy showed a firm, white, multinodular right atrial tumor with plaque like pericardial infiltration (arrow) and obstruction of the superior vena cava (*Reproduced with permission from Grebenc ML, Rosado de Christenson ML, Burke AP, Green CE, Galvin JR. Primary cardiac and pericardial neoplasms: radiologic-pathologic correlation. Radiographics 2000;20:1073–103; Figure 30 A and C*). (**c**) The tumor shows large neoplastic cells with vesicular chromatin and small amount of pale eosinophilic cytoplasm (**d**) Immunohistochemical stain for CD 20 established B cell lineage

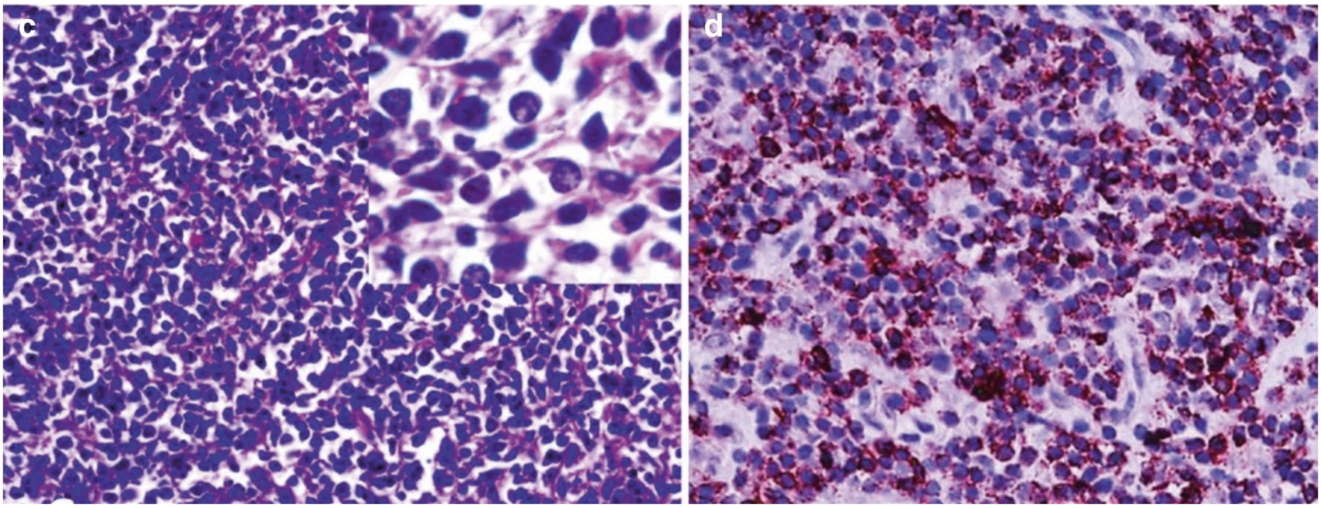

Fig. 74.10 (continued)

The differential diagnosis of low-grade lymphoma is post-transplant lymphoproliferative disorder, which is a heterogeneous infiltrate of reactive lymphocytes. Occasionally, cardiac lymphoma may clinically mimic cardiac rejection, and the histologic distinction between lymphoma and rejection may be difficult on endomyocardial biopsy [126].

Conclusion

Patients affected with cardiac tumors often present with cardiovascular compromise or embolic phenomena and exhibit cardiomegaly at chest radiography. Benign cardiac tumors typically manifest as intracavitary, mural, or epicardial focal masses, whereas malignant tumors demonstrate invasive features and may involve the heart diffusely. Benign lesions can usually be successfully excised, but patients with malignant lesions have an extremely poor prognosis.

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Concomitant Coronary Artery Disease and Lung Cancer

75

Wilhelm P. Mistiaen

High Yield Facts

- The Society of Thoracic Surgeons (STS) database reports a 20.9% incidence rate of coronary artery disease (CAD) in patients undergoing pulmonary resection for primary lung cancer.
- Despite an important clinical issue there is lack of evidence from randomized controlled trials and most data are in the form of retrospective case series.
- Historically, the preferred method for the treatment of patients with both operable CAD and pulmonary disease was a staged procedure. The cardiac procedure was typically performed first, followed by the pulmonary resection once the patient had recovered from the cardiac operation.
- Combined procedures are best suited for patients with early stage lung cancer and CAD not requiring emergent intervention.
- Certain lung resections, such as left lower lobectomy, may be more difficult to perform via a median sternotomy.
- Relative contraindications to pulmonary resection via median sternotomy include chest wall involvement, high bleeding risk, and extensive intrathoracic adhesions.
- Mediastinal lymph node dissection of certain lymph node stations, such as posterior paraesophageal and inferior pulmonary ligament nodes, may be more difficult when performed through a sternotomy.
- There is no clear evidence that extracorporeal circulation increases the risk of metastatic disease in patients with pulmonary malignancy.
- Off-pump coronary artery bypass grafting seems to mitigate the risk of bleeding and perioperative mortality compared with on-pump combined procedures. This may be related to improved results or reflect a bias in patient selection.

Introduction

Coronary artery disease (CAD) is one of the most common cardiovascular conditions. The 2016 *Heart Disease* and Stroke Statistics update of the AHA reported that 15.5 million people in the USA have *CAD*. The reported *prevalence* increases with age for both women and men. The lifetime risk of developing *CAD* with at least two major risk factors is 37.5% for men and 18.3% for women [1]. For lung cancer, it is estimated that in 2018, there will be about 234,000 new cases with about 154,000 deaths in the US [2]. Both conditions increase with age and share some risk factors such as smoking. Therefore, one can expect both conditions to occur simultaneously. During the work-up of a patient with a treatable lung carcinoma, an asymptomatic cardiac disease might be documented, or conversely, an X-ray of the chest of a cardiac patient might reveal a pulmonary malignancy. It is also important to keep in mind that pulmonary disease and the type of patients are changing. The centrally located squamous carcinoma is decreasing, while the more peripherally located adenocarcinoma is on the increase. Moreover, patients are becoming older and have more chronic obstructive pulmonary disease. Since adenocarcinoma of the lungs can be multifocal, tissue preservation is all the more important [3].

This chapter focuses on patient population with treatable concomitant CAD and lung cancer and addresses the following

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questions for the cohort of patients who are deemed operable for both conditions.

- What is the preferable strategy? Should a concomitant or staged procedure be offered?
- How—in case of a staged procedure—to deal with adhesions?
- In case of a single stage procedure, will the use of extracorporeal circulation (ECC) be necessary and what are its advantages/drawbacks? This will be of importance in cases of difficult location of the lung cancer such as in the left lower lobe.
- Will a median sternotomy suffice or are more incisions necessary, especially if the posterior mediastinal nodes need dissection?
- Can additional techniques such as video-assisted thoracoscopy (VATS) be useful in this setting?
- How much pulmonary tissue needs to be resected?

Concomitant or Staged Procedure

If the choice has been made to undertake a *staged procedure*, most authors agree to perform the cardiac operation first, because of the high risk for major adverse cardiac events such as ischemia and mortality during pulmonary surgery [4]. Recent myocardial infarction and unstable coronary artery disease are a contraindication for pulmonary surgery [5]. This approach has been proven to be safe and effective, with a morbidity and mortality rate lower than the combined procedure [6–9]. Kanzaki et al. reported lower complication rate for staged procedure (31%) compared to simultaneous surgery (45%) [10]. The staged procedure allows the patients to recover between the operations. The interval between both operations varies between 1 week and 2 months [11, 12] but intervals of more than 6 months have been recorded. Need for transfer to another center for the cardiac procedure often causes delay. However, with improved peri- and postoperative care, intervals can be kept low, especially if no ECC has been used [10]. Furthermore, there is no clear relation between the interval between the operations and the cancer recurrence rate and metastasis [11, 13]. However, by delaying the treatment of pulmonary cancer, there is always a risk that this condition might progress into an incurable disease [4]. Especially patients whose malignancy does not allow postponement could benefit from the concomitant procedure. The staged procedure has several other disadvantages. It requires two operations, each with the associated surgical trauma, need for anesthesia, risk of bleeding and need for blood transfusion and possible complications including atelectasis, pneumonia and acute renal dysfunction [5]. For patients, this means two episodes of pain and need for rehabilitation, with a certain amount of stress and anxiety between both operations.

The *concomitant procedure* has been proven to be feasible in a small series of patients with severe heart disease and lung tumors. Short-term mortality, morbidity and re-exploration for bleeding in small series are absent to low [14, 15]. Long-term results are dependent on the stage of malignancy. Furthermore, the one stage procedure reduces costs and stay in hospital and intensive care unit [5, 11]. The surgical trauma, however is more severe, with an increased risk for bleeding [5]. The exposure of dorsal lymph nodes in the posterior mediastinum may be problematic. Concomitant surgery with ECC may not be warranted in complex pulmonary procedures such as sleeve resection and vascular reconstructions [5]. In one series, of 18 cardiac patients with incidentally detected pulmonary nodules, a wedge resection was performed during the heart operation. Fifteen of these patients had a pulmonary carcinoma but in only five patients, a more radical procedure was performed at a later stage. The cardiopulmonary function in the remaining ten patients was considered too poor for a more aggressive approach. Nevertheless 3-year disease-free survival was 74% and 5-year overall survival was 46% [16].

Impact of Adhesions on Staged Procedure

After prior cardiac surgery, there is always the theoretical risk of adhesions and hence a risk for bleeding or for injury to the grafts [17]. This is more of a concern if the internal mammary artery (IMA) graft has been used and when the pleural cavity has been opened. The use of VATS is sometimes advocated [17] but this technique is universally not well received if CAD is present [18]. However, there is agreement that a cuff of lung tissue can be left around a graft in order to protect it against surgical trauma, without adverse oncologic outcome. This also applies to an IMA graft [19–21].

Use of Extracorporeal Circulation

The effect of the ECC on the immune system and on inflammation is far from resolved. Contact between blood and artificial surfaces of the device as well as hypothermia might be involved. Pro-inflammatory interleukins (IL) IL-1, IL-6, IL-8, TNF-α, and heat shock protein-70 are activated by the ECC while complement is consumed [22–25]. Other factors such as IL-10 and TGF-β1, which downregulate inflammation are also affected by the device [23, 24]. The timing of the activity is also of importance: IL-2 is decreased in the first 24 h after surgery, but increases during the following 3 days [23, 24]. Moreover, it is not easy to disentangle the effects of the trauma induced by the operation itself, the use of ECC and of blood transfusion. Probably, the surgery is the major factor, with the ECC contributing to it [22]. The ECC also affects the cellular components of the immune system. Natural killer [NK] cells are a first line defense against dissemination of malignancies by their cytotoxic activity. An increase of their activity has been documented in one report [26] but this was not confirmed by others [15, 17]. Suppression of NK cells was also observed after other surgical interventions. CD8+ cytotoxic cells showed an increase after cardiac surgery [26], but this observation is not universal [23]. CD4+ helper cells and hence the CD4+/CD8+ ratio showed a decrease in the first week of heart surgery [23, 24]. These changes also affect the postoperative immune status. Additionally the use of ECC carries the risk for postoperative bleeding, pulmonary dysfunction and potential dissemination of the malignancy [27]. According to some, the ECC may cause an inflammatory response and immune alterations, but not necessarily tumor dissemination [5].

Kanzaki et al. [10] reporting their 20-year experience of managing patients with concomitant cardiac disease and lung cancer showed that there is no clear association between the use of ECC, mortality, morbidity and more specific postoperative pulmonary complications. These data should be interpreted with caution, since these patient groups are small and variations are wide. Kauffmann et al. [4] reported an interesting comparison of the use of ECC to treat two groups of patients with cardiovascular disease and early (T1 or T2) and advanced (T4) non-small cell lung cancer. Although both groups were small, short term mortality after combined surgery with use of ECC was comparable, but the mid-term mortality was better in the T1/T2 group. Death was due to tumor recurrence in the T4 group and of cardiovascular nature in the T1/T2 group [4]. This comparison illustrates the feasibility of the one stage procedure with ECC. It also illustrates the different biological behavior of pulmonary tumors.

Off-Pump Coronary Artery Bypass Grafting

Several investigators have advocated for combined pulmonary resection and off-pump coronary artery bypass grafting in patients requiring both procedures. When looking at the studies investigating this topic, there are several common themes. Off-pump coronary artery bypass grafting when combined with pulmonary resections, results in a low risk of bleeding (0–8%), perioperative mortality (0%) as well as satisfactory long-term survival (55–75%) [5, 28–30].

Dyszkiewicz and colleagues [28] in 2004 presented 13 patients who had off-pump coronary artery bypass grafting followed by lung resection. Patients received a mean of 1.7 grafts but were not candidates for endovascular intervention. Despite no heparinization, one patient (8%) required reoperation for bleeding. There were no perioperative mortalities in this study. The investigators recommended combining operations when the coronary artery surgery can be done first, off-pump, and the patients only require one or two grafts.

A subsequent study by the same group evaluated 25 patients who had combined surgeries between 2001 and 2006. Twenty patients had a sternotomy and four had a left thoracotomy. All patients had off-pump coronary artery bypass grafting prior to lung resection. One patient (4%) had a reoperation for bleeding and one patient (4%) developed a bronchopleural fistula. There were no perioperative deaths and the 3-year survival rate was 50%. The only factor shown to have an impact on long-term survival was cancer recurrence, which was seen in 55% of the patients in this study. Preoperatively they excluded patients with N2 disease; however, two patients were discovered to have N2 disease on final pathology and did well after receiving adjuvant treatment [29].

Recently, Ma and colleagues [5] published their 12-year experience with 34 patients undergoing off-pump coronary artery bypass grafting and pulmonary resection. They excluded patients from analysis if the final pathology was not primary lung cancer. A greater number of their patients presented with pulmonary complaints than cardiac (65%). Early patients in their series were repositioned after off-pump coronary artery bypass grafting via median sternotomy and then had a lung resection via thoracotomy. Later they transitioned to performing lobectomies through the sternotomy with the assistance of a thoracoscope, predominantly for lymph node dissection. Compared with their patients who received off-pump coronary artery bypass grafting alone, the addition of a pulmonary resection did not increase their overall rate of complication (21%), which included respiratory complications and arrhythmias. There was no perioperative bleeding requiring reoperation or mortality. Three-year and 5-year survival rates were 75% and 67%, respectively.

Tourmousoglou and colleagues [30] published a best evidence topic on the subject in 2014 and included 15 retrospective studies from 1994 to 2012. They concluded that combined procedures can be safely performed in patients with stage I and stage II lung cancers; however, there are high-risk patients who likely would be better served by staged surgeries. Long-term survival is most dependent on the patients' cancer stage. They noted that off-pump coronary artery bypass grafting seemed a safe method for combined operations. They also found an aggregate mortality rate for off-pump combined operations of 0–6.6%. The risk of bleeding in these patients ranged from 0% to 4%, and 5-year survival ranged from 13% to 68%. Their data suggested that when ECC is used, the pulmonary resection should be performed first.

Choice of Incision for Access

For a cardiac procedure, which is usually performed first, a median sternotomy is widely used. But this incision is not the classic approach for pulmonary operations, since it might be difficult to reach dorsal lymph nodes [4] or the left lower lobe [17]. The use of IMA grafts could also hamper the dissection of the mediastinal nodes. This could be alleviated by using only the IMA graft from the opposite side. If necessary, an extension of the same incision or even a second incision can be used. If adhesions are absent, the use of VATS allows a good view of the operative field, including the pulmonary hilum and the mediastinum [5]. The latter is necessary for lymph node dissection, which is necessary for tumor staging and for prognosis. A one-sided thoracotomy can be used in specific cases: a left sided thoracotomy is feasible in patients with a one-vessel LAD disease while a right-sided thoracotomy can be used in patients with a one-vessel right coronary artery disease [5].

Extent of Pulmonary Resection

A clear margin of resection is emerging as the standard of care in pulmonary operations [3]. The use of preoperative positron emission tomography/CT scanning and endobronchial ultrasonography can document the presence or absence of nodal spread of the cancer. Rigorous intra-operative staging and improved technology for dividing pulmonary parenchyma have also altered the approach [3]. Much depends also on the pulmonary reserve of the patients. If this reserve is impaired and the tumor is still confined [less than 1 cm], it seems reasonable to perform a limited resection. Early results seem to indicate that overall and disease specific survival is not decreased [31], but this observation is not universal. One should also take into account that pulmonary adenocarcinoma can be multifocal. These difficult procedures should be performed in high-volume specialized centers with the necessary diagnostic expertise. Lobectomy should remain for now the standard until the newer guidelines of cancer societies have been published.

Conclusions

- In case of resectable pulmonary cancer in a patient with CAD, every effort should be made to treat both heart and lung disease.
- The choice between a concomitant and staged operation is less clear, but for oncologic reasons, a single stage operation seems preferable.
- The use of ECC should be discouraged for reasons of inflammation, immunosuppression, bleeding and potential tumor spread. However, this is often not possible.

Due to ethical reasons there are no randomized controlled trials available on this subject. Current best available evidence is in the form of retrospective, small case series. Selection bias, referral bias, treatment bias and survival bias cannot be ruled out. The most appropriate approach is to tailor the treatment according to the patient's status taking into consideration the expertise available in individual centers and more importantly of the individual surgeon.

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Trauma to the Heart and Great Vessels

Ankur Bakshi, Matthew J. Wall Jr., and Ravi K. Ghanta

High Yield Facts

- Thoracic trauma, with the potential for injury of the heart or great vessels, is associated with high morbidity and mortality.
- The most common operation in patients with thoracic trauma is tube thoracostomy and laparotomy.
- Unstable patients with agonal vital signs may undergo a resuscitative left anterior thoracotomy in the emergency center.
- Drainage of 1500 mL on insertion or 200 ml per hour of blood can be an indication for an operative thoracotomy.
- Computerized tomographic angiography for blunt aortic injury can have a sensitivity of 98% and specificity of 100% and can guide surgical planning, particularly if endovascular treatment is planned.
- Pre-hospital mortality for penetrating cardiac injury is high, with up to 90% of patients dying at the scene.
- Anatomically, the right ventricle is the most anterior cardiac structure and it is the one that is most commonly injured in stab wounds to the heart (60%), followed by the left ventricle (37%) and right atrium (13%).
- Penetrating injury to the coronary artery carries a very high mortality (69%).
- Nearly 80% of patients with blunt aortic injuries die on scene.
- Other life-threatening injuries, such as intra-cranial, splenic or pelvic injuries, should be addressed first in stable patients with blunt aortic injury.
- Carotid injuries can be associated with aerodigestive injuries which may also require attention and can increase the risk of repair blowout.
- Cardiopulmonary bypass is rarely required to repair injuries of the heart and great vessels.

Introduction

Thoracic trauma, with the potential for injury of the heart or great vessels, is associated with high morbidity and mortality [1]. Clinical suspicion of injury, with logical and sequential evaluation, followed by timely intervention is required to optimize survival. Despite great emphasis, heart and great vessel injuries are actually uncommon after thoracic trauma. Notably, the most common operation in patients with thoracic trauma is tube thoracostomy and laparotomy [2]. Thus, a high clinical index of suspicion is required for timely diagnosis. Although trauma has traditionally been managed by general surgeons, a growing body of literature supports more frequent involvement of cardiothoracic surgeons, particularly in the management of complex thoracic injuries [3].

Initial Evaluation

Initial evaluation should follow Advanced Trauma Life Support (ATLS) protocols, followed by focused imaging. Clinical signs of thoracic injury include chest wall contusion and penetrating wounds involving the upper torso.

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Previously, the "cardiac box," bounded by the mid-clavicular lines, xiphoid process, and clavicles, was thought to predictive of penetrating cardiac injury, but recent studies have shown this to be a poor predictor [4]. Thus, one should be cognizant of the possibility of a major vessel injury for any upper torso penetrating trauma. Figure 76.1 illustrates an evaluation and management algorithm based on the Western Trauma Association guidelines [5]. Unstable patients with agonal vital signs may undergo a resuscitative left anterior thoracotomy in the emergency center. This allows for release of tamponade, hemorrhage control, and, in some cases, repair. If possible, a chest X-ray and ultrasound should be performed as this can aide in diagnosis. Pneumothorax or hemothorax are managed with tube thoracostomy. Drainage of 1500 mL on insertion or 200 ml per hour of blood can be an indication for an operative thoracotomy. For stable patients, additional diagnostic studies include electrocardiogram (ECG), computerized tomography (CT), CT angiography (CTA), angiography, echocardiography, and cardiac catheterization, depending on the clinical suspicion. CT scanning has become ubiquitous, but should not result in a delay in definitive surgical management. The additional

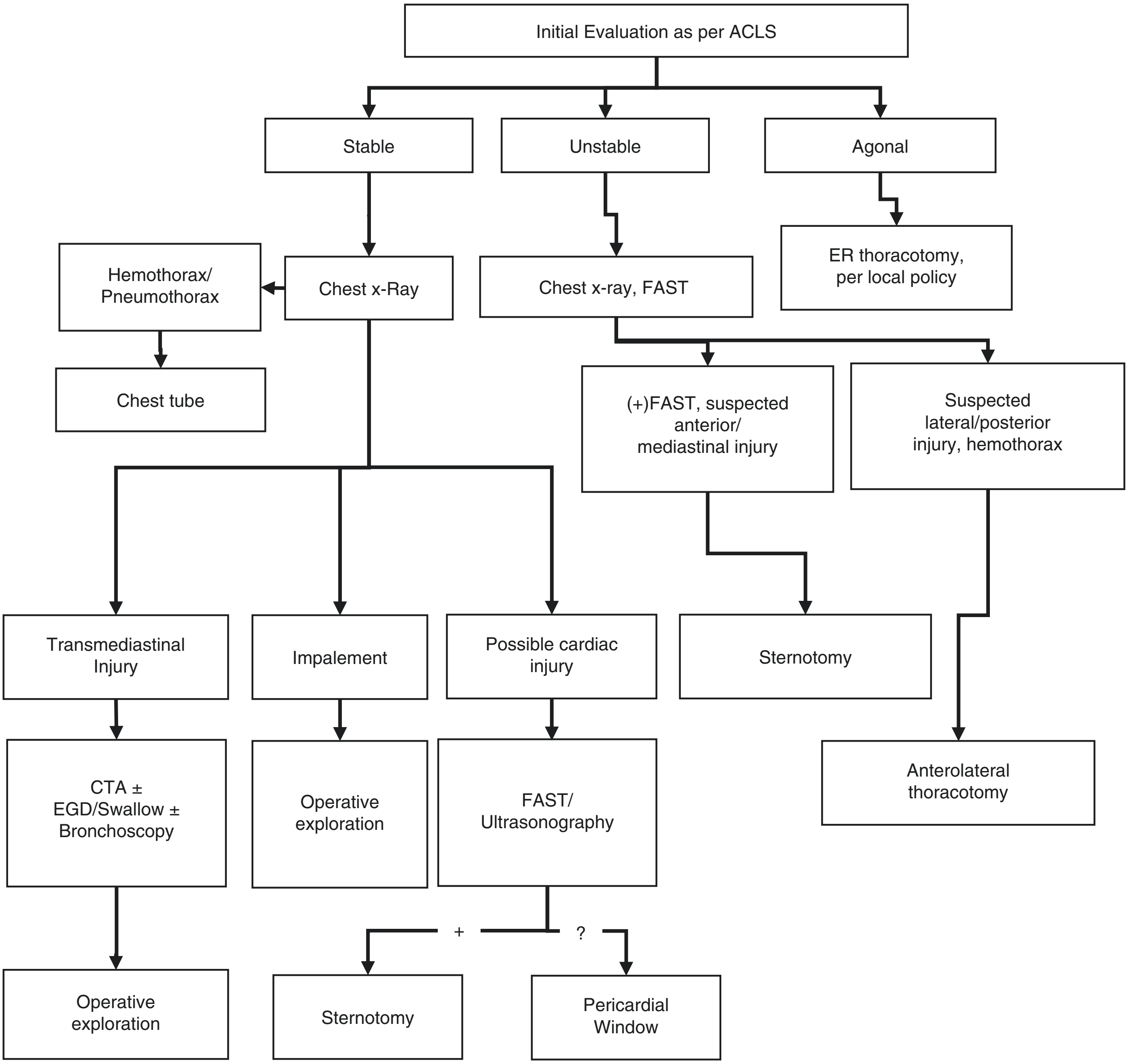
Initial Evaluation as per ACLS
Stable
Unstable
Agonal
Hemothorax/ Pneumothorax
Chest x-Ray
Chest x-ray, FAST
ER thoracotomy, per local policy
Chest tube
(+)FAST, suspected anterior/ mediastinal injury
Suspected lateral/posterior injury, hemothorax
Transmediastinal Injury
Impalement
Possible cardiac injury
Sternotomy
CTA ± EGD/Swallow ± Bronchoscopy
Operative exploration
FAST/ Ultrasonography
Anterolateral thoracotomy
+
?
Operative exploration
Sternotomy
Pericardial Window

Fig. 76.1 Evaluation algorithm for patient with penetrating thoracic trauma. *ACLS* advanced cardiac life support, *CTA* computerized tomographic angiography, *EGD* esophagogastroduodenoscopy, *FAST* focused assessment with sonography in trauma. (Adapted from Karmy-Jones et al. [5], with permission)

information provided with CT scans can be very valuable, especially for evaluation of suspected great vessel injury and missile trajectory. CTA for blunt aortic injury can have a sensitivity of 98% and specificity of 100% and can guide surgical planning, particularly if endovascular treatment is planned [6].

Evaluation and Management per Structure Injured

Heart

Surgical Approach

The optimal surgical incision depends on associated injuries and clinical scenario. Although median sternotomy is the primary incision for cardiac surgeons, left anterior thoracotomy, with a "clamshell" extension may be more appropriate. Left anterior resuscitative thoracotomy is the preferred approach in the emergency department. Bleeding from cardiac wounds can be controlled with temporizing measures including finger occlusion, Foley balloon tamponade, or use of a surgical stapler [8]. Extension of the thoracotomy through the sternum, a "clamshell" thoracotomy, allows for wide access to both thoracic cavities and the mediastinum. A left thoracotomy approach has the added advantage of descending aortic cross clamping if required. A median sternotomy can be considered in patients who are not expected to require descending aortic repair or clamping.

Penetrating Cardiac Injury

Pre-hospital mortality for penetrating cardiac injury is high, with up to 90% of patients dying at the scene. Patients arriving with signs of tamponade are more likely to survive than those arriving with signs of exsanguination [7]. Anatomically, the right ventricle is the most anterior cardiac structure and it is the one that is most commonly injured in stab wounds to the heart (60%), followed by the left ventricle (37%) and right atrium (13%) [4]. Gunshot wounds are associated with multi-chamber injuries to the heart compared to stab wounds [4]. Definitive repair of most cardiac wounds can be performed without cardiopulmonary bypass utilizing suture cardiorraphy with a 4-0 Polypropylene suture. Interrupted felt buttress mattress sutures can also be placed. If necessary, a pericardial patch can be placed over the site to provide additional hemostasis. Penetrating wounds near coronary arteries should be repaired with a deep horizontal mattress suture that runs beneath the artery to avoid narrowing or ligation.

Following repair, presence of additional cardiac injury should be carefully assessed, including the use of transesophageal echocardiography if possible. Not uncommonly, traumatic ventricular septal defects (VSDs), atrial septal defects (ASDs) and valvular injuries are diagnosed post-operatively [8]. They are often associated with multichamber injuries. As ASD and VSD repairs are done with cardiopulmonary bypass, definitive repair may be delayed until control of other associated injuries and adequate resuscitation [8]. In many cases, ASD or VSD may not be apparent on initial echocardiogram. If a delayed repair is required, the ASD or VSD may be best exposed by re-opening the penetrating cardiac wound to expose the septal defect, rather than the traditional trans-valvular approaches [9]. ASD and VSD repairs can then be performed in standard fashion.

Coronary Artery Injury

Penetrating injury to the coronary artery carries a very high mortality (69%) [8]. Coronary injuries are most frequently ligated. Proximal lesions of the left anterior descending (LAD), right coronary artery (RCA), and circumflex (Cx) may require a coronary artery bypass. The LAD is the most common injured artery, followed by the RCA. In cases of distal injuries to the LAD, RCA, or Cx, or injury to any branch diagonal or obtuse marginal arteries ligation is often the most appropriate strategy [8]. In the event of coronary artery ligation, consideration should be made for insertion of an intra-aortic balloon pump to support the heart during this iatrogenic transmural myocardial infarction [8].

Blunt Cardiac Injury

Blunt cardiac injury (BCI) was previously described as myocardial contusion; however, this nomenclature was changed due to its lack of specificity [10]. The diagnosis of blunt cardiac injury remains difficult. Isolated evaluation with ECG has not proven sufficient to rule out blunt cardiac injury [10]. Isolated troponin-I levels have been studied and remain controversial for the diagnosis of blunt cardiac injury. Only 49% of patients with a positive troponin were found to have blunt cardiac injuries [11]. However, a normal troponin did have a high negative predictive value, particularly when combined with a normal electrocardiogram [12]. Echocardiography is commonly used for the diagnosis of blunt cardiac injury to evaluate for structural damage. In admitted trauma patients with unexplainable hypotension, new onset arrhythmias, or cardiogenic shock, even with normal troponins and electrocardiograms, blunt cardiac injury should be considered and echocardiography is recommended [12]. Patients with evidence of blunt cardiac injury should be observed in a telemetry unit or the intensive care unit. Most dysrhythmias can be observed. Patients with intramural hematomas can also be observed without surgical intervention, as they will resolve [11].

Post-discharge monitoring of these patients is important as late sequelae can develop. These sequelae include atrial or ventricular septal defects, valvular injury or dysfunction, ventricular pseudoaneurysm, cardiac-vascular fistulas, conduction abnormalities, poor ventricular function/heart failure, intramural hematomas, pericarditis/endocarditis, and pericardial effusions [13]. The incidence of these complications varies by series and is likely underreported; however, it remains that post-operative echocardiography is a useful tool for identification of these delayed complications [13].

Aorta

Penetrating Aortic Injury

Management of a suspected penetrating aortic injury will be dictated by patient status and suspected injury location. In an unstable patient, immediate surgical exploration is necessary. In the unstable patient, empiric incisions are often a best determination based on injury trajectory. For suspected injury to the ascending aorta and arch vessels or anterior midline structures, a median sternotomy can be performed. Extension superiorly can facilitate exposure of the proximal innominate artery and the carotid arteries [14]. Patients in extremis may already have undergone a resuscitative thoracotomy in the emergency department. While this incision allows for access to the descending thoracic aorta, it does not provide access to the ascending aorta or the arch vessels and extension to a clamshell thoracotomy may be necessary [14]. Other incisions include the posterolateral thoracotomy for the descending aorta, high anterolateral thoracotomy for exposure of the subclavian artery, or supraclavicular incisions for the exposure of the subclavian or innominate artery.

In the stable patient, diagnosis can be made with CT or angiography. Aortography may also be used, with the caveat that small injuries may be obscured by a column of contrast [14]. In these patients, endovascular repair has been described for the descending thoracic aorta [15].

Blunt Aortic Injury

Like blunt cardiac injuries, blunt aortic injuries are often a result of rapid deceleration such as in motor vehicle collisions or falls from height and occur at points of tethering, such as at the aortic isthmus. Nearly 80% of patients with blunt aortic injuries die on scene [16]. Patients with blunt aortic injuries often have a large burden of other injuries, including rib fractures, pulmonary contusions, hemothorax, orthopedic fractures and head trauma [17]. In stable patients, aortic repair is often undertaken in a delayed fashion unless there are high risk features such as pseudoaneurysm or active extravasation [16]. Other life-threatening injuries, such as intra-cranial, splenic or pelvic injuries should be addressed first. Anti-impulse therapy is considered, similar to type B dissection [17].

Repair may be done either by open approach or through endovascular approaches. Endovascular techniques for repair of these injuries has become increasingly popular [6]. An open approach is performed via posterolateral thoracotomy. Open repair is associated with a higher risk of paralysis and mortality, when compared to endovascular repair, but a lower risk of stroke [16]. When planning for endovascular repair, one must be cognizant of the need for an appropriate seal zone for the device. Additionally, given that most of these injuries occur at the aortic isthmus, there is a risk that the seal zone may overlie the subclavian artery. This may require a carotid-subclavian bypass, fenestrating the stent graft ex vivo [18], or fenestrating the stent graft in vivo with an intravascular laser [19]. Additionally, care must be taken when sizing the endograft. The patients are typically young with compliant aortas that can vary in diameter depending on the cardiac cycle. Intravenous ultrasound may be an adjunct in assisting with sizing [20]. Endovascular repair requires serial follow up with CT scans to evaluate for endoleaks.

Innominate Artery

Penetrating Innominate Artery Injury

Given the innominate artery's location, penetrating injuries to the innominate artery tend to also involve other structures, such as the trachea, innominate vein, carotid artery and superior vena cava [21]. Many of these patients present in shock [21, 22]. Often, temporizing measures, such as balloon tamponade, may be necessary while bringing the patient to the operating room. In the unstable patient, immediate exploration is required to control hemorrhage. Median sternotomy or median sternotomy with right supraclavicular can be used to gain proximal and distal control to repair such injuries [22]. Repair options include suture repair, interposition repair, aorto-innominate bypass or, in extreme cases, ligation [21, 22]. Endovascular repair has also been described, particularly in the stable patient.

Blunt Innominate Artery Injury

Blunt innominate artery injuries are caused by pinch injuries between the sternum and spine [14]. The injury tends to be an intimal tear at the origin of the vessel. Aorta-innominate bypass is the repair technique of choice and can often be performed without cardiopulmonary bypass or deep hypothermia [21].

Carotid Artery

Penetrating Carotid Artery Injury

Injuries to the carotid artery are divided by zone based on location. Zone I injuries occur below the sternal notch, zone II injuries between the sternal notch and the angle of the mandible and zone III injuries are above the angle of the mandible. Signs of carotid injury include external bleeding, rapidly expanding hematomas, thrill/bruits, loss of carotid pulse and neurologic deficits [22]. Assessing and securing the airway should be a priority. For zone II injuries, exposure can often be achieved with an anterior neck incision. For zone I injuries, a median sternotomy may be necessary to obtain proximal control. For zone III injuries, distal control is often difficult and may require subluxation of the jaw. Fogarty balloon occlusion may allow for temporary control of the injury and allow for time to stabilize the patient [22]. In extreme cases, carotid ligation may be necessary; however, this method has a high risk of stroke.

In the stable patient, a CTA of the neck may be used to diagnose carotid injury. In the stable patient, in addition, endovascular techniques can be considered for repair of the injury. One must be cognizant that carotid injuries can be associated with aerodigestive injuries which may also require attention and can increase the risk of repair blowout [22].

Blunt Carotid Artery Injury

Blunt carotid injury is an underdiagnosed injury, often only being caught after the patient's develop neurologic signs or symptoms. Various screening criteria, including the modified Denver and Memphis criteria exist [23]. With the improvements in technique, CTA has become the recommended screening tool for blunt carotid artery injury, although four vessel cerebral angiography remains the gold standard. These injuries are graded as per the Denver grading scale. For grade 1 injures, anti-thrombotic therapy with either heparin drip or aspirin may be used, if the patient does not have a contraindication such as a head injury [23]. Grade II–V may be repaired with either open surgical or endovascular techniques.

Subclavian Artery

The subclavian artery poses a challenge, owing to the difficulty accessing the vessel to obtain proximal and distal control. An important surgical maneuver for obtaining proximal control is to obtain control proximal to the hematoma. For right subclavian injuries, median sternotomy with right supraclavicular extension provides appropriate exposure. For left subclavian injuries, a "trapdoor" incision combining a left thoracotomy, sternotomy, and supraclavicular incision was previously advocated, but largely abandoned due to its morbidity. Left anterior lateral thoracotomy in the third or fourth intercostal space allows exposure for proximal control [14]. A supraclavicular incision then allows for distal control and repair. Repair may include suture repair or interposition grafts with Dacron, PTFE or saphenous vein. If damage control is necessary, the vessel may be ligated with definitive repair within 24–48 h [24].

Given the location of the subclavian artery, endovascular repair offers an attractive alternative to avoid sternotomy or thoracotomy. Gilani and colleagues described a technique where proximal control was established with balloon occlusion via femoral access [25]. Distal control was obtained from the brachial artery and wire access into the aorta was established. This allowed for stent graft repair and image guided thrombectomy.

Conclusion

Management of cardiac or great vessel injury can be challenging in trauma patients. Clinical suspicion of injury, appropriate diagnostic studies, and expeditious surgical intervention is required. Cardiopulmonary bypass is rarely required to repair most injuries. Familiarity with surgical exposure via median sternotomy, clamshell or left thoracotomy is required to successfully repair injuries. The role of endovascular intervention, as an important tool in the management of great vessel trauma, is increasing.

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Pericardial Diseases

77

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High Yield Facts

- The pericardium is formed from two layers, visceral and parietal.
- These two layers are separated by approximately 15–35 ml of plasma ultrafiltrate that fills the pericardial space.
- Pericardial thickness varies from 0.8 to 1.0 mm on anatomical specimens and 0.7–1.2 mm in computed tomography or 1.5–2.0 mm in cardiac magnetic resonance imaging.
- The most frequent cause of relapsing pericarditis is inadequate medical therapy in the initial episode.
- The most relevant causes of effusive pericarditis are inflammation, malignancy, and renal failure.
- Only approximately 1.8% of patients with effusive pericarditis subsequently develop constriction.
- For most patients with constrictive pericarditis in Western countries, etiology of the disease is unknown (idiopathic) and presumed to be the sequela of viral infection.
- In other parts of the world, tuberculosis as a cause is as frequent as idiopathic.
- Pericardiectomy is indicated for the treatment of chronic constrictive pericarditis, effusive disease with need for tissue or fluid samples, effusive-constrictive disease, or relapsing pericarditis that fails to improve with medical therapy alone.
- Early mortality is approximately 5% for patients having pericardiectomy for constrictive pericarditis.

Anatomy and Functions of Pericardium

The pericardium is formed from two layers, visceral and parietal. The visceral pericardium is the innermost, a mesothelium-derived monolayer that joins with epicardium and reflects off the great vessels into the serosal layer of the parietal pericardium. The parietal pericardium consists of a tough fibrous component and a serosal layer that closely binds the adventitia of the great vessels, cervical fascia, central diaphragmatic tendon and less tightly to the esophagus and descending aorta [1, 2]. Pericardial thickness varies from 0.8 to 1.0 mm on anatomical specimens and 0.7–1.2 mm in computed tomography (CT) or 1.5–2.0 mm in cardiac magnetic resonance imaging (MRI).

These two layers are separated by approximately 15–35 ml of plasma ultrafiltrate that fills the pericardial space. Apart from this space, there are sinuses and recesses that allow pericardium to accommodate for changes in fluid volume either in the pericardial space or intracardiac hemodynamic changes. For example, the oblique sinus is limited by the pulmonary veins laterally, parietal pericardium posteriorly, left atrium anteriorly and inferior vena cava inferolaterally; the transverse sinus is delimited anteriorly by the aorta, main pulmonary artery, posterolaterally by atria, their appendages and the superior vena cava. Sensory innervation is thought to be carried out by the phrenic nerve; these include pressure and mechanical sensation [3], as well as pain [1].

Mechanical function of the pericardium minimizes external influences such as respiration and positional changes, as well as limitation of cardiac distention while allowing chamber coupled interactions. Other functions such as metabolic, vasomotor, fibrinolytic, immunologic, and ligamentous are out of the scope of this chapter.

The only other structure within pericardium is epicardium, composed of fatty tissue covers most of the atrioventricular, interventricular grooves, and right ventricle free wall. Epicardium covers the coronary vessels and contains nerves and lymphatics [1].

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Etiology of Pericardial Diseases

There are many etiologies of pericardial diseases, some of which can be inferred from clinical information such as duration of symptoms, history of prior infections or autoimmune disease, etc. For the purposes of this chapter, we will divide etiologies according to the likelihood that surgical intervention will be required; a complete list of etiologies can be found in Table 77.1.

Chronic Relapsing (Recurrent) Pericarditis

The diagnosis of chronic relapsing or recurrent pericarditis includes repeated episodes of pericarditis after a symptom-free period of at least 4–6 weeks. On occasions, symptoms persist without a clear asymptomatic period; these patients suffer from incessant pericarditis, while others experience symptom persistence beyond 3 months and are classified as having chronic relapsing pericarditis [4]. The most frequent cause of relapsing pericarditis is inadequate medical therapy in the initial episode [4, 5].

Table 77.1 Etiologies of pericardial diseases[a]

Infectious	**Viral**: Enteroviruses (Coxsackie, Echovirus), Herpesvirus (EBV, CMV, HHV-6), Adenoviruses, Parvovirus B19
	Bacterial: Mycobacterium tuberculosis (most common), Coxiella burnetti, Borrelia burgdorferi
Non-infectious	**Autoimmune (most common)**: Systemic autoimmune (SLE, Sjögren's syndrome, RA, Systemic sclerosis), Systemic vasculitides (like eosinophilic granulomatosis with polyangiitis, allergic granulomatosis, etc.), Sarcoidosis, Inflammatory bowel disease
	Neoplastic: Primary tumors (pericardial mesothelioma), Metastatic tumors (lung, breast cancer and lymphoma)
	Metabolic: Uremia, Myxedema, Anorexia nervosa
	Traumatic and Iatrogenic: Early onset: Direct Injury (penetrating thoracic injury or esophageal perforation), Indirect injury (non-penetrating thoracic injury, radiation) Delayed onset: Postmyocardial infarction, Postpericardiotomy syndrome
Other	Amyloidosis, Aortic dissection, Pulmonary arterial hypertension, Chronic heart failure
	Congenital partial and complete absence of pericardium

CMV cytomegalovirus, *EBV* Epstein-Barr virus, *HHV-6* Human herpes virus 6, *RA* rheumatoid arthritis, *SLE* systemic lupus erythematosus

[a] Adapted from [4]

Underlying etiologies commonly associated with relapse are idiopathic pericarditis, viral infections either new or reactivated, and autoimmune diseases. The incessant form of pericarditis is more common in those who receive steroid-based treatment [6]. Unfortunately, there is no accurate way of predicting recurrences.

When evaluating a patient with possible recurrent pericarditis, it is important to confirm the diagnosis by documenting recurrence of pericardial pain and the signs listed in Table 77.2. Patients should then be assessed for high risk features such as fever and large pericardial effusion that might prompt in-hospital treatment or earlier invasive procedures. Finally, consideration should be given to possible etiologies missed in the first episode of pericarditis which might require different medical therapy, such as malignancy, systemic inflammatory diseases, or tuberculous infection [7].

In general, surgical management of relapsing pericarditis is underutilized and unnecessarily delayed because of the paucity of clinical studies and the perceived benign nature of the disease. Approximately 25% of patients with acute non-infectious pericarditis have at least one episode of relapse [6, 8]. Although most patients are adequately treated medically for their initial relapse and often are never symptomatic again, a subset of patients experience chronic relapsing pericarditis. The disease may not be life-threatening, but it can have a substantial effect on quality of life due to discomfort as well as side effects of medication. Current recommendations for management of relapsing pericarditis include treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) and colchicine for the initial relapse. Corticosteroids may then be used for patients in whom initial medical therapy has failed; in some cases, immunosuppressive agents are indicated for patients in whom an autoimmune or inflammatory disease is the underlying cause [4]. Although the use of corticosteroids for relapsing pericarditis can relieve symptoms, chronic use may lead to steroid dependence and unwanted side effects [7].

Table 77.2 Pericardial syndromes[a]

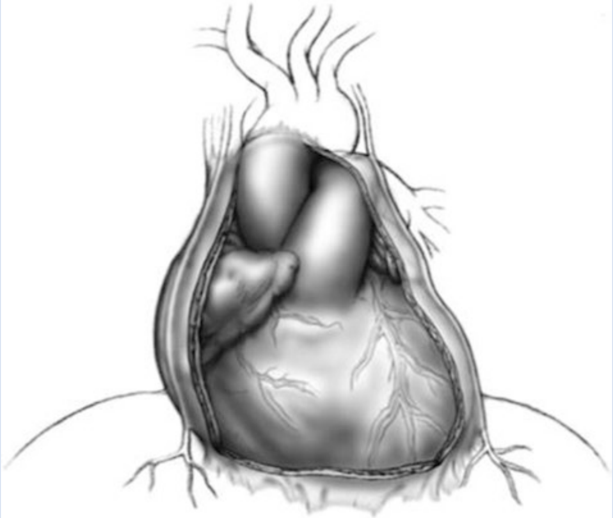
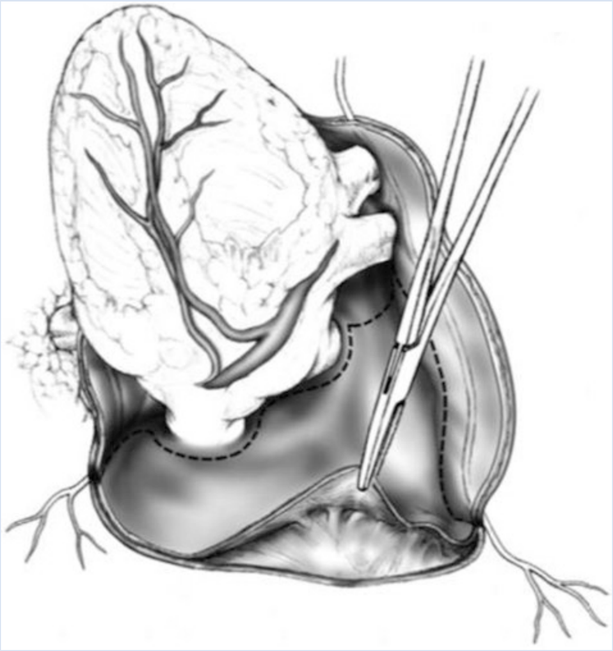
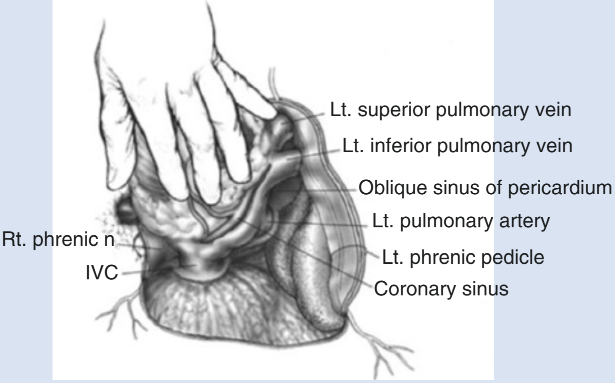
Syndrome	Presentation	Criteria	Treatment
Pericarditis	Acute <4 weeks	At least two of the following: 1. Pericardic chest pain 2. Pericardial rub 3. Electrocardiographic signs 4. Pericardial effusion Additional: • Elevated markers of inflammation (ESR, CRP) • Pericardial inflammation evident on Imaging (CT, CMR)	• Aspirin: 750–1000 mg tid for 1–2 weeks • Ibuprofen: 600 mg tid for 1–2 weeks • Colchicine: 0.5 mg daily (<70 kg) or 0.5 mg bid (>70 kg)
	Incessant	Symptoms continue >4–6 weeks but <3 months	• Similar to above but continue until symptom improvement and taper
	Recurrent	Symptom resurgence after remission period of at least 4–6 weeks	
	Chronic	Symptoms persist >3 months	

CRP C-reactive protein, *CMR* cardiac magnetic resonance, *CT* computed tomography, *ESR* eruthrocyte sedimentation rate

[a] Adapted from [4]

In a previous study [9], we examined morbidity and mortality of patients who undergo pericardiectomy, and compared outcomes to patients who only received medical treatment. Patients in the surgical group were more likely to take colchicine and corticosteroids and more likely to have had previous pericardiotomy. At operation, complete pericardiectomy was performed as described below in Table 77.3. As seen in Fig. 77.1, there was no significant difference in

Table 77.3 Definitions of pericardiectomy

Pericardiectomy	Resection extent	Imaging
Anterior	Between phrenic nerves	
Complete	Anterior plus diaphragmatic surface resection	
Radical	Complete plus posterior to the left phrenic nerve	 Lt. superior pulmonary vein Lt. inferior pulmonary vein Oblique sinus of pericardium Lt. pulmonary artery Rt. phrenic n Lt. phrenic pedicle IVC Coronary sinus

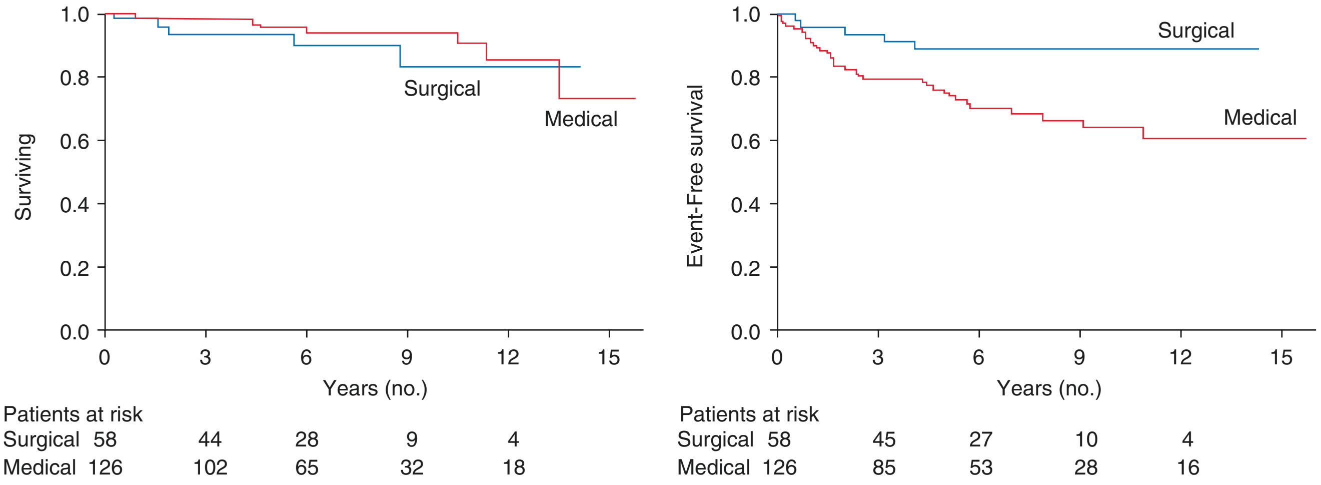


Fig. 77.1 Comparison of survival and relapse rates in patients with recurrent pericarditis who underwent pericardiectomy vs. medical management only. (**a**) Kaplan-Meier curve for survival in patients with pericardiectomy vs. medical management for relapsing pericarditis (p = 0.26). (**b**) Kaplan-Meier curves for relapse in patients with pericardiectomy vs. medical management for relapsing pericarditis (p = 0.009). (Reproduced with permission from [9])

overall mortality (8 year survival 91% in the surgical group vs. 93% in the medical treatment group), but recurrences were far less common following pericardiectomy [five patients (8.6%) vs. 36 patients (28.6%) p = 0.009] with a mean time to relapse of 2.1 years. It is important to note that medically managed patients treated with any duration of corticosteroids were more likely to have a relapse compared with those who were not treated with corticosteroids.

Because patients with relapsing pericarditis rarely develop constrictive pericarditis, surgical treatment is often considered as a last resort. We believe, however, that operation should be discussed earlier with patients who have relapsing pericarditis because of the safety and efficacy of pericardiectomy. Earlier intervention will decrease morbidity, improve functional status, while avoiding medication dependence and side effects.

Effusive Pericardial Disease

Effusive pericarditis stems from excess fluid accumulation. Either exudates, transudates or fresh blood limit diastolic filling, decrease ventricular preload and cardiac output. Symptoms arise once fluid accumulation exceeds pericardial stretch capacity and cardiac volumes become decreased [10, 11], in the acute setting this can be life threatening, while in chronic effusions the pericardium stretches and can accommodate larger fluid volumes.

While the list for etiologies of pericardial diseases is long, the most relevant in the effusive subgroup are inflammatory causes, malignancy, and renal failure. Effusions can present as acute, subacute and chronic problems with or without tamponade. Echocardiographic criteria for classifying pericardial effusions are size, mild (<10 mm), moderate (10–20 mm) and large (>20 mm), and their distribution, loculated or circumferential. Some patients may have effusive/constrictive disease in which constrictive features persist after fluid removal.

Acute symptoms of effusive pericarditis may include sharp, stabbing retrosternal pain worsened by recumbency and improved by sitting forward. Other clinical findings are tachycardia, hypotension, pulsus paradoxus, increased jugular venous pressure, and muffled heart sounds. A subset of patients may present with cardiac tamponade, and characteristic features initially described by Beck are the triad of muffled heart sounds, arterial hypotension, and venous distention [12]. The surface electrocardiogram can show nonspecific findings such as electrical alternans, widespread ST segment, or T wave abnormalities. The chest X-ray may show an enlarged cardiac silhouette, and serum inflammatory markers can also be increased.

Diagnosis of a pericardial effusion is confirmed by cardiac imaging, transthoracic echocardiography and/or chest CT. The more chronic forms of cardiac tamponade due to effusive pericarditis may mimic features of right ventricular dysfunction with lower extremity edema, abdominal distention, and ascites, characteristics also common in constrictive pericarditis [10, 13]. Clinical findings of pericardial effusion are summarized in Table 77.4.

Most patients with non-malignant effusive pericarditis have a good prognosis and respond to anti-inflammatory therapy with low rates of progression to constrictive pericarditis; indeed, only approximately 1.8% of patients with effu-

Table 77.4 Pericardial effusion—presentation, symptoms, and initial management

Presentation	Clinical findings	Management
Timing: • Acute • Subacute • Chronic	• Pleuritic chest pain • Progressive orthopnea • Tamponade physiology • Nausea, vomit, dysphagia, hoarseness, hiccups, cough, weakness, fatigue	• Hospitalize • Consider drainage if tamponade or large • Treat underlying cause, Inflammatory, infectious or neoplastic
• Circumferential • Loculated		
Size: • Mild <10 mm • Moderate 10–20 mm • Large >20 mm		
Nature: • Exudate • Transudate		

Table 77.5 Risk factors for poor prognosis with pericardial effusions[a]

Criteria	Clinical predictors
Major	Fever >38
	Subacute onset
	Large effusion
	Cardiac tamponade
	Lack of response to medical therapy after at least 1 week
Minor	Myopericarditis
	Immunosuppression
	Trauma
	Oral anticoagulant therapy

[a]Adapted from [4]

sive pericarditis subsequently develop constriction [14]. There is, however, a subset of patients with effusive pericarditis who may require in-hospital treatment and drainage procedures. High risk clinical features include fever, subacute onset, large pericardial effusion, tamponade presentation, and lack of response to anti-inflammatory therapy, summarized in Table 77.5. Other characteristics that may prompt hospitalization and invasive procedures are myopericarditis, immunosuppression, trauma, or oral anticoagulation [4, 6] (Table 77.6).

When pericardial drainage is necessary due to hemodynamic compromise or failure of medical management, echocardiographic-guided pericardiocentesis is the preferred initial procedure and is definitive treatment in more than 90% of patients [15, 16].

Surgical drainage can be performed thoracoscopically, through a small left intercostal incision, or through a subxyphoid pericardiotomy. Although effusions can be relieved by creation of a pericardial window, we prefer to perform a wide pericardiectomy to reduce risk of recurrent fluid accumulation and/or subsequent constriction. In an earlier report, Piehler et al. studied 145 patients with pure pericardial effusions, who received either a complete (50%), partial (25%) or window procedures (25%) due to benign and malignant etiologies. Although there was no difference survival of patients in the treatment groups, all recurrences requiring reoperation occurred in patients who had initial pericardial window (Fig. 77.2). Freedom from reoperation and chance from operative failure were worse for the pericardial window group when compared to partial or complete pericardiectomy ($p < 0.001$) patients [17].

Constrictive Pericardial Disease

For most patients with constrictive pericarditis in Western countries, etiology of the disease is unknown (idiopathic) and presumed to be the sequela of viral infection. In other parts of the world, tuberculosis is as frequent as idiopathic [18]. Constriction following cardiac surgery and radiation induced pericardial disease appear to be increasing in prevalence in surgical series [13, 19, 20].

The presentation of pericardial constriction may be transient, associated with effusion, or chronic with variable degrees of pericardial calcification. Transient constrictive pericarditis is most commonly seen in patients post-cardiotomy but may also be seen with autoimmune diseases or idiopathic cases. Abnormal hemodynamics in these patients usually improve and/or resolve spontaneously or with NSAIDs. Effusive-constrictive pericarditis is the combination of pericardial effusions and constriction physiology. Finally, calcific constrictive pericarditis accounts for about 25–30% of constrictive cases, and is common in patients with radiation-induced or tuberculous pericarditis [21].

Constrictive pericarditis results from formation of fibrous adhesions between the visceral and parietal layers of the pericardium. This may be accompanied by calcium deposition, and the resulting encasement of the myocardium interferes with the normal diastolic and systolic function. Mechanical interference with proper diastolic ventricular filling reduces ventricular stroke volume and increases end-diastolic ventricular pressures and atrial pressures. With chronic constriction, there may be variable degrees of myocardial atrophy that can further worsen cardiac output and lead to ventricular dysfunction early after relief of constriction [22].

Abnormal cardiac function associated with constrictive pericarditis can be identified by examining alterations in hemodynamics during the respiratory cycle. In normal conditions, the changes in intrathoracic pressure lead to similar changes in pericardial and intracardiac pressures, and cause a normal slight variation in the left ventricular stroke volume and arterial systolic blood pressure. The negative intrathoracic pressure of inspiration favors increased venous return to the right heart and mildly reduces left ventricular

Table 77.6 Step-by-step pericardiectomy

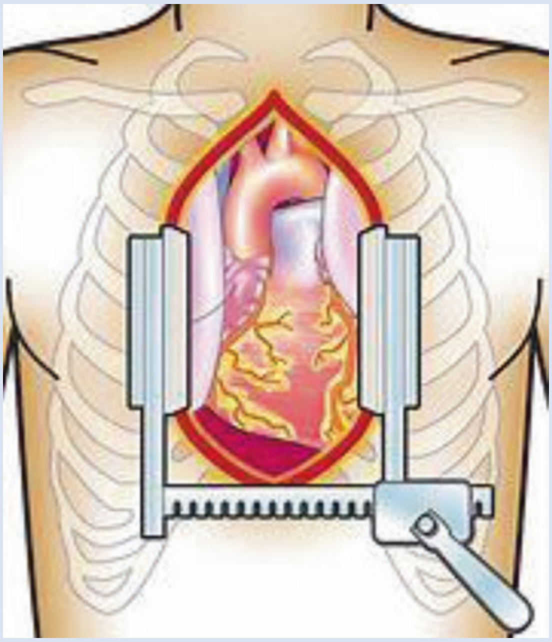
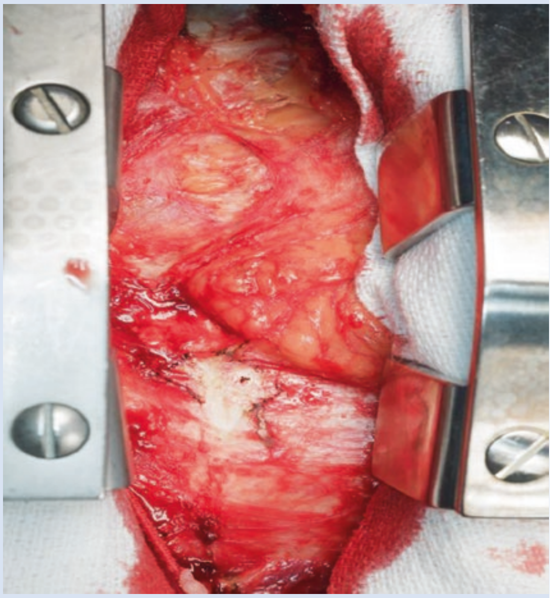
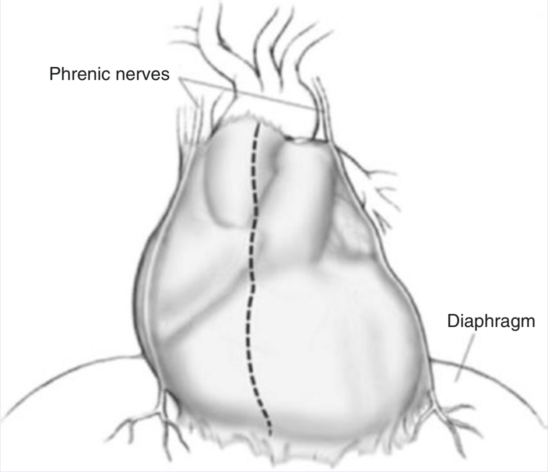
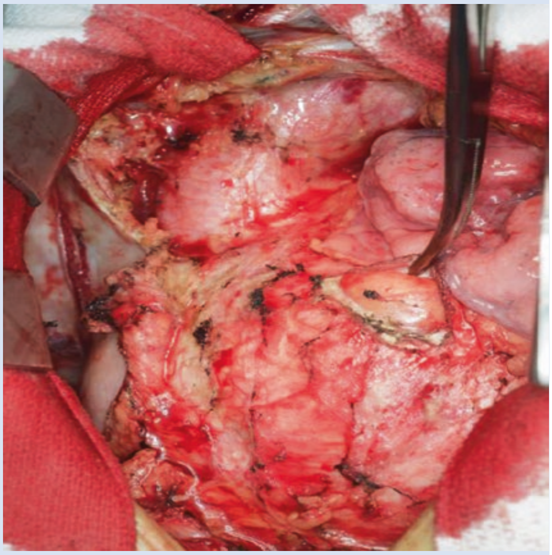
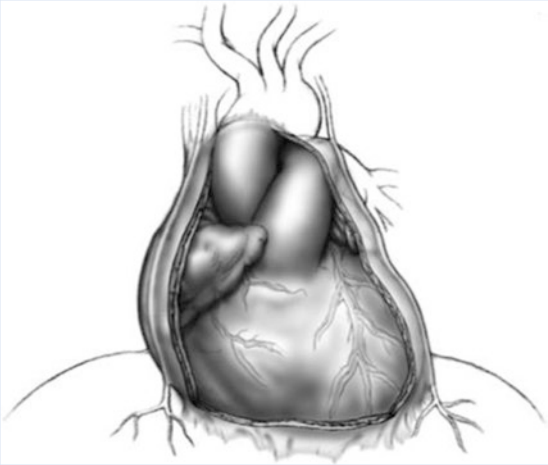
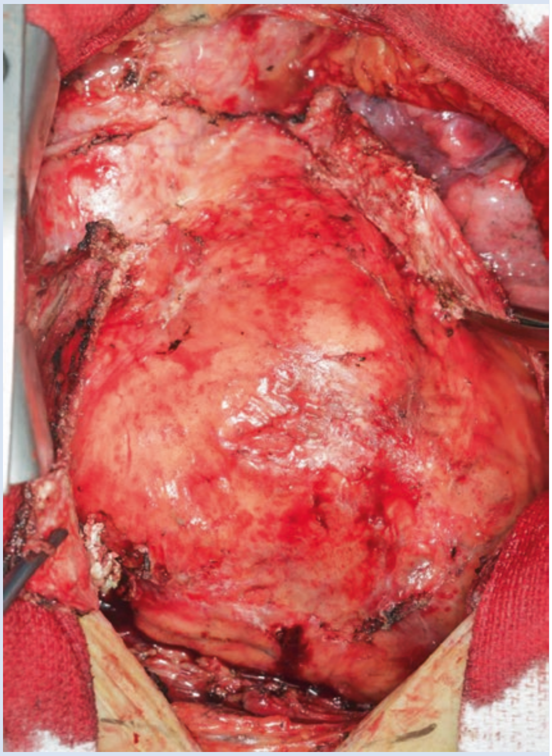
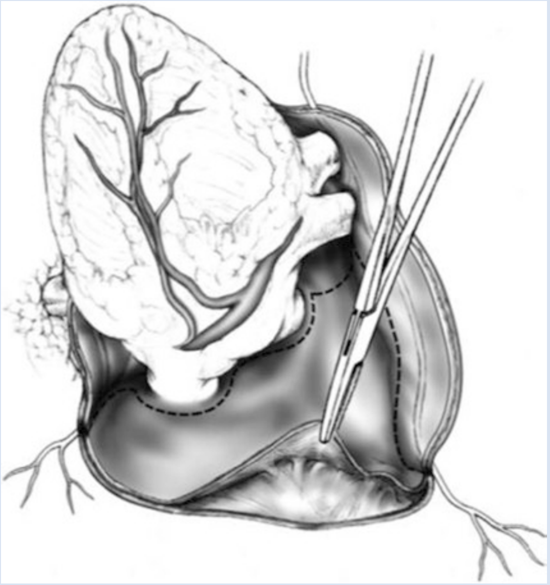
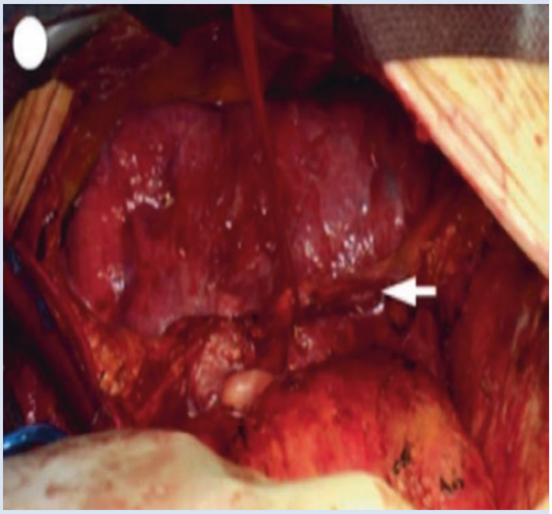
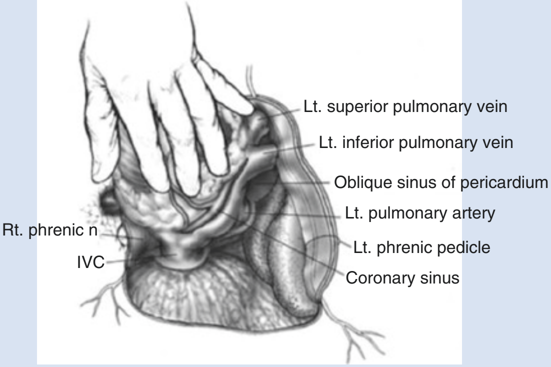
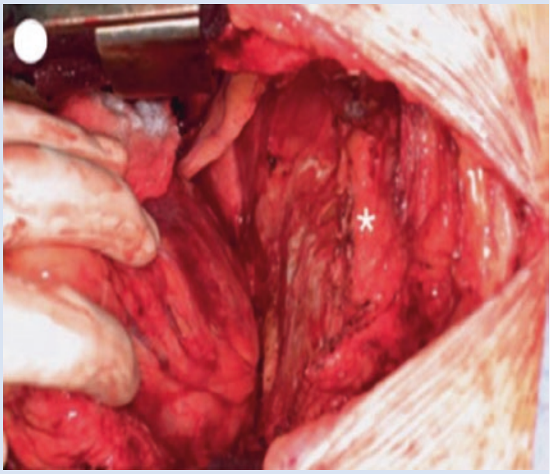
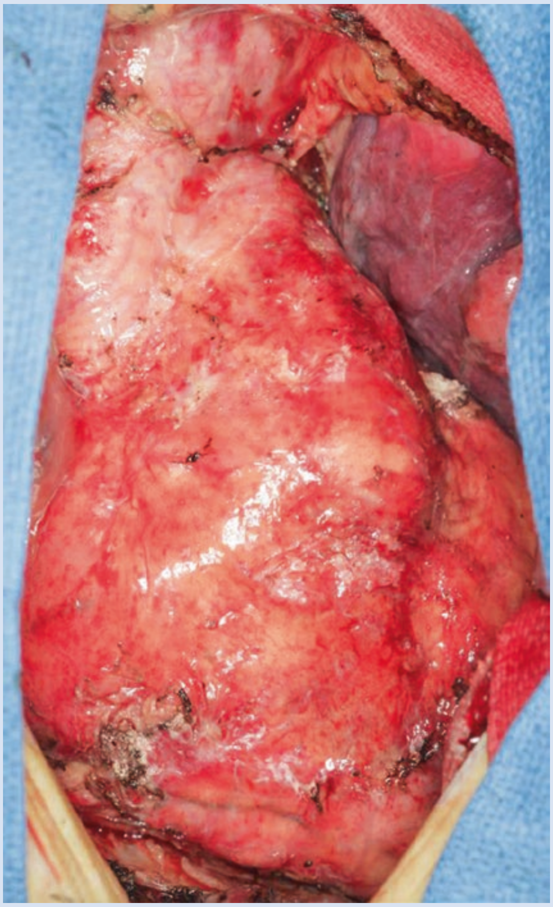
Step	Imaging	Intra-operative photograph
Median sternotomy or Thoracotomy		
Conduct a midline incision of the pericardium from the aortic reflection down to the diaphragmatic surface		

Table 77.6 (continued)

Step	Imaging	Intra-operative photograph
Perform anterior pericardiotomy from midline incision to 1–1.5 cm medial to right phrenic nerve and laterally from midline to left phrenic nerve. Scoring the anterior pericardium from aortic reflection to the diaphragmatic pericardium		
Dissect lateral to left phrenic nerve medially until about 1 cm above the entrance of pulmonary veins		

(continued)

Table 77.6 (continued)

Step	Imaging	Intra-operative photograph
Dissect pericardium overlying diaphragm freeing the left and right ventricular inferior surfaces. Separating pericardium from muscular and fibrous diaphragm*	 Lt. superior pulmonary vein Lt. inferior pulmonary vein Oblique sinus of pericardium Lt. pulmonary artery Rt. phrenic n Lt. phrenic pedicle IVC Coronary sinus	
Final product		

filling and stroke volume. In constrictive pericarditis, however, this respiratory variation in cardiac filling and output becomes exaggerated. With inspiration, the right ventricle cannot expand to accommodate increased venous return, rather, right ventricle expands into the left ventricle, via a shift of the ventricular septum. This leads to decreased left ventricular compliance, and end-diastolic volume, limiting stroke volume. Pulsus paradoxus is the manifestation of the abnormal fall of systolic blood pressure during inspiration. Non-compliance of the right ventricle also leads to paradoxical rise of the JVP with inspiration (Kussmaul sign) [23, 24]. Some of these hemodynamic changes are illustrated in Fig. 77.3.

The pulmonary veins are extra pericardial and experience an inspiratory pressure decrease in contrast to greater pressures in the left heart chambers due to the septal shift.

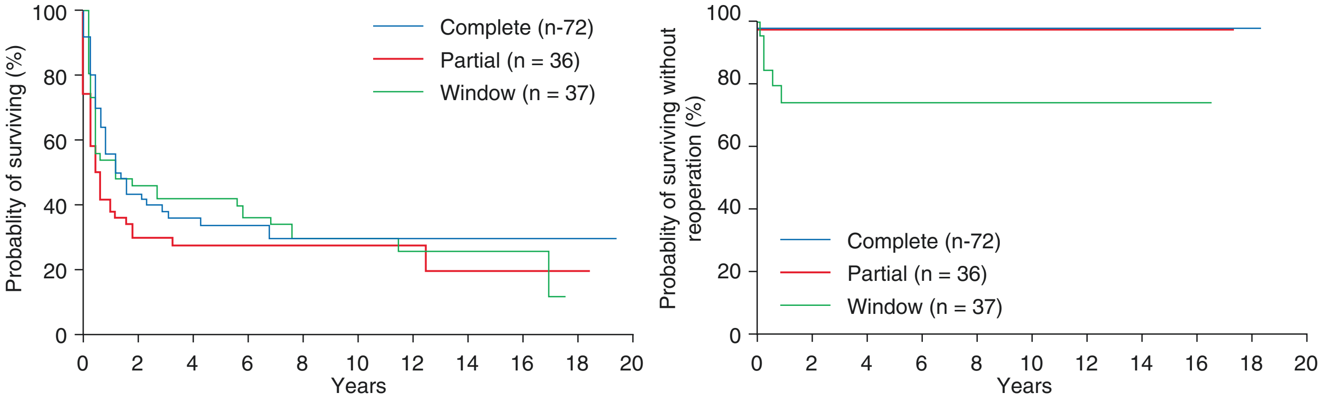


Fig. 77.2 Comparison of survival and freedom from reoperation in patients with effusive pericarditis who underwent surgical management. (**a**) Kaplan-Meier curve comparing survival of patients who underwent surgical management for malignant and benign disease. (**b**) Kaplan-Meier curve comparing the influence of type of pericardiectomy on freedom from reoperation. (Reproduced with permission from [17])

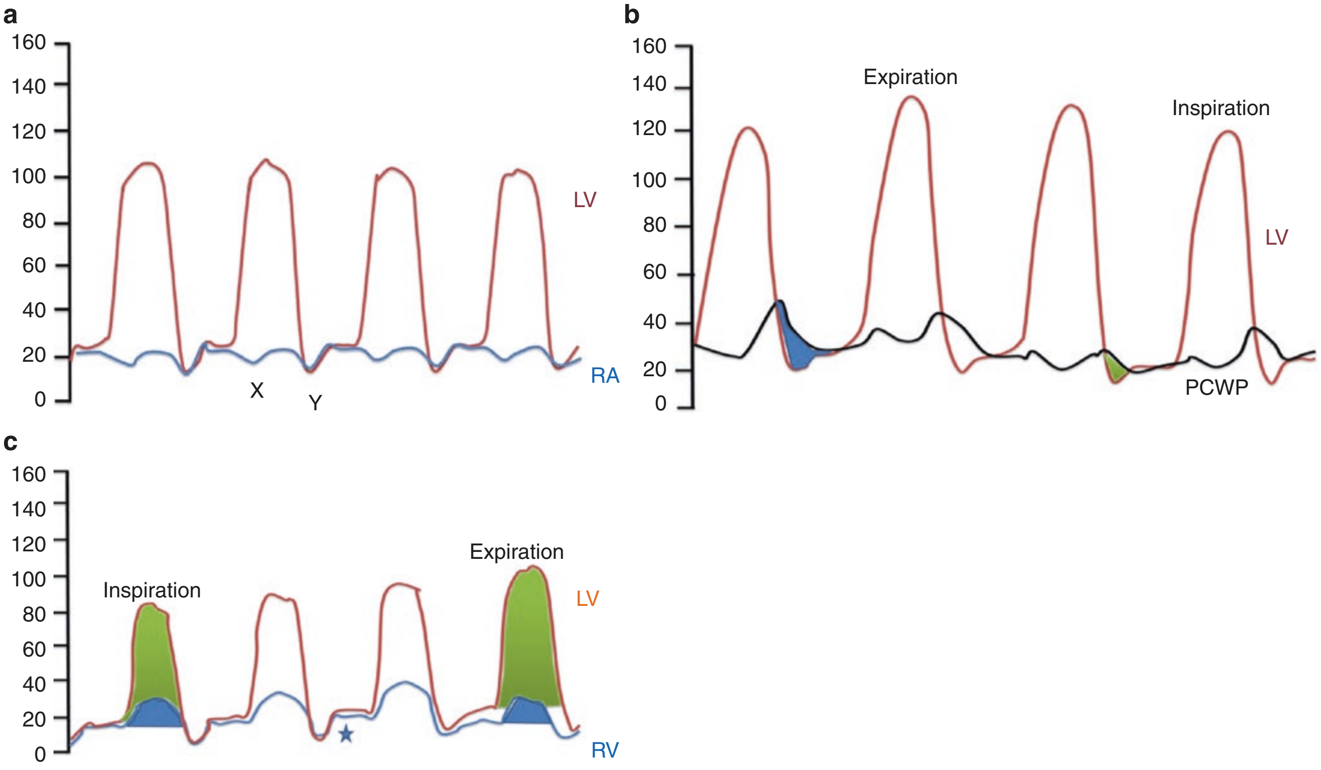


Fig. 77.3 Cardiac catheterization findings in constrictive pericarditis. (**a**) Right atrial (RA) and left ventricular (LV) tracings. (**b**) Left ventricular and pulmonary artery wedge pressures (PCWP). (**c**) Simultaneous left ventricular and right ventricular (RV) tracings for ventricular discordance. (∗) signals square root sign. (Reproduced with permission from [27, 52])

Increasing pressures in the left ventricle during diastole coupled with lower pressures in the pulmonary veins impairs diastolic filling; this phenomenon is termed dissociation of intrathoracic and intracardiac pressures.

Expiration, in normal conditions, increases intrathoracic pressures and allows increasing left atrial and ventricular filling; the ventricular septum shifts rightward. In constrictive pericarditis, the increasing venous return from pulmonary veins augments left ventricular (LV) end-diastolic volume, causing exaggerated ventricular septal shift and reduced right ventricular (RV) filling. This will increase right atrial pressures and result in venous flow reversal that can be seen during echocardiography as expiratory hepatic vein flow reversal [13, 25, 26].

Clinical characteristics of constrictive pericarditis can be subtle in early stages and, thus, there should be a high index of suspicion for patients with symptoms of right heart failure, normal valvular anatomy and ventricular function limitation out-of-proportion to echocardiographic findings [27]. In patients with previous cardiac operations the diagnosis of constriction may be delayed because of suspicion that the clinical problem is related to pre-existing cardiac disease. However, predictors and mechanisms for prevention of constriction following cardiac operations have not been established [28].

Classically, patients present with symptoms of low cardiac output such as weakness, fatigue, worsening functional status and/or problems related to systemic venous hypertension, including lower extremity edema, ascites and hepatomegaly. Often, patients with constrictive pericarditis and ascites are misdiagnosed as having chronic primary liver disease. Other important findings on clinical examination include decreased pulse pressure, jugular venous distention, hepatomegaly, Kussmaul's sign, hyperdynamic non-displaced apical impulse, and prominent RV impulse (parasternal heave). On auscultation, the heart sounds may be diminished or muffled, and there may be a pericardial knock (high-pitched early diastolic filling sound) [27].

Echocardiography is the preferred imaging technique and may establish the diagnosis without need for further studies. Characteristic echocardiographic findings are respiratory-related ventricular septal shift (bounce), reversal of the normal relationship of mitral lateral e′ and medial e′ velocities (annulus reversus), and prominent hepatic vein expiratory diastolic flow reversal. The respiratory septal shift is an important finding that when coupled with either of the two other findings, produce a sensitivity for diagnosis of 87% and specificity of 91% [21, 27].

Hemodynamic cardiac catheterization can aid in identification of constriction when the diagnosis is in doubt from echocardiographic examination. Classical findings include elevation of right atrial pressure, rapid diastolic filling, and equalization of end-diastolic pressures in all four cardiac chambers (Fig. 77.3a). More recent criteria use hemodynamic variations with the respiratory cycle to aid in identification of constriction. The respirophasic oscillations of stroke volume seen in constriction are due to fixed pericardial volume, enhanced ventricular interdependence, and dissociation of intrathoracic and intracardiac pressures. The latter is seen as the decrease in the wedge to left ventricular pressure gradient during inspiration (Fig. 77.3b) [29]. Furthermore, documentation of a gradient difference (expiratory minus inspiratory wedge to left ventricular gradient) ≥5 mmHg is 93% sensitive and 81% specific for constriction [30]. Ventricular interdependence is seen by changes in RV and LV pressures with inspiration where there is an increase in the area of the RV pressure curve paired with a decrease in the LV pressure curve. A systolic ratio (area of the RV to LV pressure curve area) in inspiration versus expiration >1.1 has a sensitivity of 97% and specificity of 100% for diagnosis of constriction (Fig. 77.3c) [31].

Other imaging modalities that can be used for diagnosis and preoperative planning in patients with constrictive pericarditis are CT and cardiac MRI. Chest CT is useful in assessing pericardial thickening and calcification. However, absence of pericardial thickening on imaging does not exclude the presence of constrictive pericarditis. As reported by Talreja et al. 18% of patients with constrictive pericarditis documented at operation had normal pericardial thickness (<2 mm). Those with normal pericardial thickness had similar hemodynamic changes and postoperative functional outcomes following pericardiectomy compared to patients with thickened pericardium [32]. Another use of chest CT is preoperative planning for identification of cardiac structures such as coronary bypass grafts that might be at risk for injury during re-sternotomy [27].

Cardiac magnetic resonance imaging may also aid in diagnosis of constriction. It is highly accurate in determining pericardial thickness >4 mm [33] and may also reveal other important clues to the diagnosis such as the presence of septal bounce. Septal bounce is a consequence of two simultaneous movements, rapid ventricular filling and atrial systole. Initially the acute tricuspid valve angle will induce blood to impact the proximal interventricular septum, causing the septum to deviate proximally and a back-movement of the tricuspid valve and right atrium; due to this back movement, blood inflow crossing the tricuspid valve strikes the distal septum distally causing a shallow movement of the distal septum during the atrial systole. Studies evaluating these phenomena have shown sensitivity from 73% to 100% and a specificity of 82–100%, with high positive and negative predictive values [34]. Further, cardiac MRI correlates well with pathologic findings of constrictive pericarditis. As shown by Young and colleagues, the presence of edema-like pericardial signal on T2-weighted images is related to the presence of neovascularization, and congestion on pathological examination [35]. In patients with constriction, CMR can also detect ventricular interdependence as quantified by the ratio of end-diastolic biventricular areas at end-inspiration and end-expiration [36].

Although noninvasive imaging can aid in the diagnosis of constrictive pericarditis, results may not be conclusive. Thus, when clinical and echocardiographic or invasive hemodynamic features indicate constriction, symptomatic patients with heart failure should not be denied pericardiectomy if they have a normal pericardial thickness seen in noninvasive imaging.

Pericardiectomy

Indications

Indications for pericardiectomy are chronic constrictive pericarditis, effusive disease with need for tissue or fluid samples, effusive-constrictive disease, or relapsing pericarditis that fails to improve with medical therapy alone. Pericardiectomy is the definitive treatment for many patients with pericardial disease but is generally underutilized or recommended late in the patient's clinical course due to difficulty in diagnosis and/or perceived high risks of morbidity and mortality associated with the procedure.

Approaches

Pericardiectomy can be performed through a variety of incisions including median sternotomy, anterolateral thoracotomy, bilateral anterior transsternal thoracotomy, or port access with or without robotic assist [37, 38]. The choice of incision depends on the underlying disease and cosmetic considerations. We prefer a median sternotomy for most patients and reserve the inframammary left anterolateral incision for women who wish to avoid a midline scar. Other authors favor a left anterior thoracotomy for pericardiectomy in patients with purulent pericarditis in order to avoid risk of sternal infection [26, 37]. A lateral approach may have disadvantages as Tokuda and associates reported an increased risk of pulmonary complications and need for prolonged ventilation with this incision [39]. A median sternotomy provides optimal exposure of the anterior and diaphragmatic portions of the pericardium and easy access to the aorta and right atrium for cannulation when extracorporeal circulation is necessary.

Use of Cardiopulmonary Bypass

We employ cardiopulmonary bypass with a beating, nonworking heart in approximately 60% of patients with chronic constrictive pericarditis who undergo pericardiectomy. The potential disadvantage of extracorporeal circulation is bleeding related to heparinization, but in most patients bleeding during dissection on bypass is minimized due to reduction in venous pressure. Further, support of the circulation permits manipulation of the heart for complete pericardiectomy and is particularly useful in dissection of calcifications that penetrate into the myocardium.

Use of cardiopulmonary bypass may also reduce the risk of excessive distention of the cardiac chambers immediately following pericardiectomy. The causes of low cardiac output after pericardiectomy are complex, but one important mechanism is over distention of the left and right ventricles when pericardial constraint is released. Many patients with chronic constriction have myocardial atrophy [22]. Muscle atrophy paired with ventricular over distention caused by excess cardiac filling may affect ventricular contractility and impair cardiac output. When operation is performed on cardiopulmonary bypass, there is no immediate ventricular distention with pericardiectomy, and during weaning from extracorporeal circulation, hemodynamics are restored with normal filling pressures thus avoiding over distension.

Technique

Dissection begins anteriorly with a midline incision in the thickened pericardium. It is important to identify the correct plane of dissection so that there is no residual epicardial constriction. The authors favor early entry into the pleural spaces so that the phrenic nerves can be identified and preserved. The anterior pericardium is reflected laterally to a point 1–1.5 cm above the right and left phrenic nerves. Some surgeons use a nerve stimulator to confirm the location of the phrenic nerve. The left ventricle is freed from the diaphragmatic pericardium and from the pericardium posterior to the left phrenic nerve.

Patients with extensive pericardial calcification may present special problems during operation, especially if areas of calcification burrow deeply into the myocardium. Dissection of these areas risks bleeding from the cardiac chamber and/or coronary artery injury. In some patients these calcific islands are avoided, and in other patients it is wise to use cardiopulmonary bypass to facilitate dissection. If areas of epicardial constriction cannot be removed safely, a series of grid-like incisions in the pericardium, "Waffle procedure" may be useful [40, 41].

To avoid residual constriction and need for repeat procedures, pericardiectomy should be as complete as possible. As mentioned previously, it is of paramount importance to dissect in correct plane and not leave residual epicardial constriction. We believe that complete pericardiectomy includes removal of the anterior and diaphragmatic portions of the pericardium. In many cases it is possible to remove pericardium posteriorly between the left phrenic nerve and the pulmonary veins. Although anterior pericardiectomy is simple to perform [42], and patients may experience some symptomatic relief, there is still a risk of residual constriction related to the diaphragmatic pericardium. Inadequate pericardiectomy is an important cause of recurrent symptoms and need for repeat procedure [43]. In addition, complete pericardiectomy is associated with improved survival compared to anterior pericardiectomy; in the study by Chowdhury et al. the 10 year survival of patients with complete pericardiectomy was 90% as compared to 75% in patients who had anterior pericardiectomy only (Fig. 77.3) [37].

Special Considerations

After pericardiectomy, most patients improve in terms of functional status [20]. Residual symptoms of right heart failure may be related to incomplete pericardiectomy, presence of myocardial atrophy, fibrosis from radiation induced heart disease, and/or associated cardiac disease [13, 43].

Patients with radiation induced constrictive pericarditis present a special challenge as they may have associated obstructive coronary artery disease, valvular dysfunction, and conduction system abnormalities [44]. Because radiation injury causes variable degrees of myocardial fibrosis [45], residual myocardial dysfunction due to restrictive physiology may not allow for a complete recovery after pericardiectomy for constrictive pericarditis. Recent investigations suggest that use of LV longitudinal, circumferential and torsional mechanics can aid in assessing the degree of restrictive cardiomyopathy from radiation-induced fibrosis and determine possible recovery from pericardiectomy alone [46]. Due to the potential difficulty in differentiating constrictive pericarditis from restrictive cardiomyopathy, we often perform concomitant prophylactic pericardiectomy for patients with radiation induced heart disease at the time of other cardiac procedures such as valvular replacement or repair and coronary bypass [44].

Tricuspid valve regurgitation (TR) is a known risk factor for late mortality in patients undergoing pericardiectomy for constrictive pericarditis [19, 47–49]. After pericardiectomy, any worsening of RV function may lead to dilation of the tricuspid annulus and progressive functional tricuspid valve leakage [50]. Indeed, in our most recent studies of patients following pericardiectomy, even mild degrees of TR impact late survival [51]. We therefore have a low threshold for concomitant tricuspid valve repair in patients with moderate degrees of TR or those who exhibit any worsening of valve leakage at the time of pericardiectomy.

Results of Pericardiectomy

The early and late outcomes following pericardiectomy are related to disease etiology and degree of preoperative disability. For example, among patients undergoing pericardiectomy for relapsing pericarditis, early mortality approaches 0% [9]. For patients having pericardiectomy for constrictive pericarditis, early mortality is approximately 5%; but operative risk is only 1% for patients in NYHA classes I or II. Similarly, early mortality was as low as 3% for patients with idiopathic etiology of constriction, compared to 14% for patients who had previous radiation. Overall survival late after pericardiectomy for constrictive pericarditis is also influenced by these same factors with reduced survival of patients of radiation induced heart disease (Figs. 77.4 and 77.5) [19].

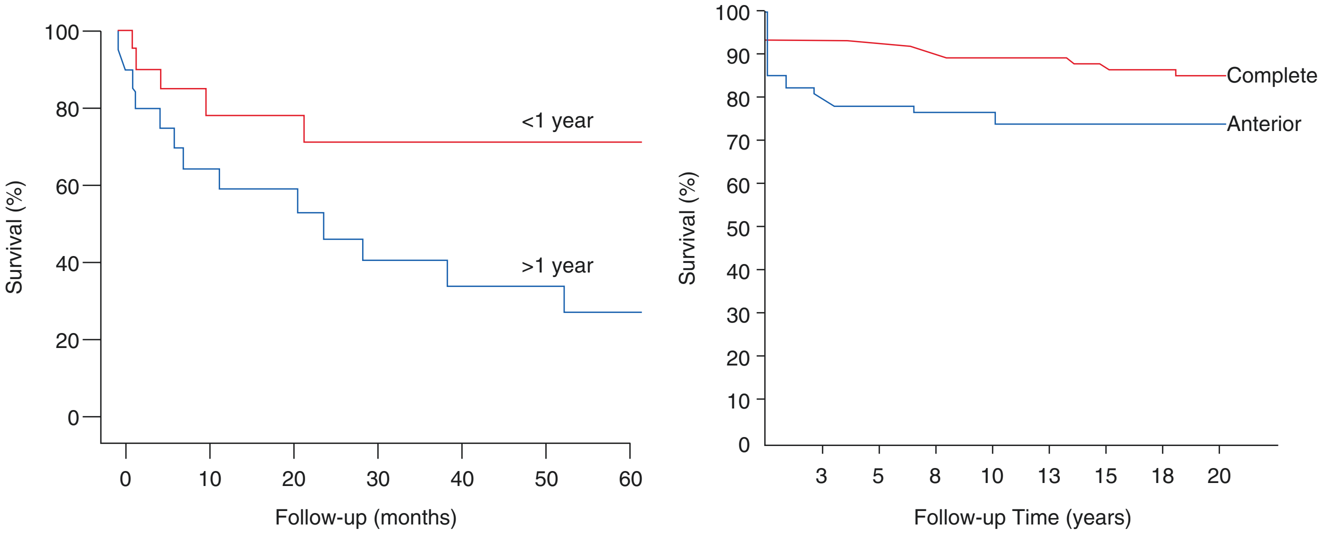


Fig. 77.4 Kaplan-Meier estimates of survival among patients with completion pericardiectomy. (**a**) Long-term survival of patients who require a completion pericardiectomy less than 1 year vs. more than 1 year after initial pericardiectomy (Reproduced with permission from [43], and patients with different extents of pericardial resection). (**b**) Long-term survival of patients with constrictive pericarditis according to their resection extension. (Reproduced with permission from [37])

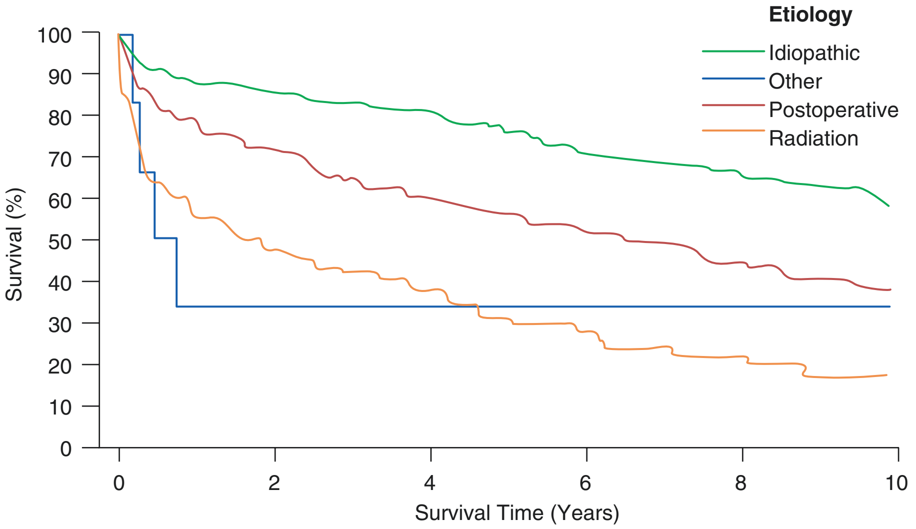


Fig. 77.5 Kaplan-Meier survival estimate among etiology of constrictive pericarditis. Long-term survival of patients with constrictive pericarditis undergoing pericardiectomy, stratified by disease etiology. (Reproduced with permission from [19])

Patients-at-risk

Idiopathic	447	248	208	152	112	74
Other	7	1	1	1	1	1
Postoperative	261	144	103	75	50	34
Radiation	92	35	24	15	10	6

Conclusion

The pericardium is simply a 2-layered membrane enveloping the heart and great vessels. The broad spectrum of syndromes involving the pericardium present with varying degrees of clinical significance, from asymptomatic presentations to life-threatening emergencies. Impaired diastolic filling of the heart represents a common theme of pericardial disease, with the rate of onset of pericardial pathology largely determining the extent of this impairment and subsequent severity of presentation. Although echocardiography is most often the first imaging modality used to assess the pericardium, CT and MRI are frequently being used to aid in diagnosis and assess response to therapy. Pericardiectomy is the definitive treatment for many patients with pericardial disease. A median sternotomy approach is preferred as it enables adequate resection and removal of the diaphragmatic pericardium and the anterior pericardium. Late outcomes depend on severity of right-sided heart failure preoperatively, the etiology of constrictive pericarditis, and adequate pericardial resection. Late results are excellent in patients with idiopathic disease or those with pericarditis secondary to prior cardiac operations. However, survival is reduced in those with radiation-induced constrictive pericarditis, primarily owing to additional secondary effects of radiation on cardiac valves, epicardial coronary arteries, and ventricular myocardium where fibrosis may cause associated restrictive cardiomyopathy.

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Pulmonary Thromboendarterectomy

78

Michael M. Madani and Jill R. Higgins

High Yield Facts

- Pulmonary thromboendarterectomy (PTE) is a technically difficult operation that involves performing a complete endarterectomy of the pulmonary arteries under profound hypothermia and circulatory arrest.
- The operation reduces right ventricular impedance, improves perfusion of ventilated lung, and is the definitive treatment for chronic thromboembolic pulmonary hypertension (CTEPH).
- Thromboembolic pulmonary hypertension is underrecognized even in the Western world; although the true incidence of this disease is unknown and hard to establish, it is estimated that roughly abut 4–5% of patients with acute PE will go on to develop CTEPH.
- More recently, advancement of surgical techniques, along with the development of new instruments, have allowed us to offer and perform a complete endarterectomy even in patients with isolated segmental and subsegmental disease.
- For those who are determined inoperable by an expert center, due to the location of the obstructive disease or significant comorbidities, newer percutaneous interventions such as Balloon Pulmonary Angioplasty (BPA) may offer a potential treatment strategy.
- Although BPA is in its infancy, and requires multiple sessions, there are encouraging early results from a few centers in Japan, Europe, and the U.S.
- Most recently, a minimally invasive approach has been developed to avoid sternotomy in highly selected patients. The procedure is currently only offered to patients with more proximal disease, suitable anatomy for mini-anterior thoracotomy, and to those with no need for concomitant procedures.

Introduction

Acute pulmonary thromboembolism and its chronic sequelae are significant causes of morbidity and mortality. However, the chronic disease process that can occur, is often underdiagnosed due to the non-specific nature of the two major symptoms, dyspnea on exertion and fatigue. Furthermore, physical findings may be elusive until symptoms of right heart failure have developed. The condition carries a high morbidity and long-term prognosis is quite poor, if the patient remains untreated [1]. Pulmonary thromboendarterectomy (PTE) or pulmonary endarterectomy (PEA) is the definitive treatment for chronic thromboembolic pulmonary hypertension (CTEPH) [2, 3]. Although, acute pulmonary embolism is one of the more common cardiovascular diseases, CTEPH is significantly underdiagnosed, and as a result PTE remains an uncommon procedure. The disease is characterized by intraluminal thrombus organization, fibrotic scar tissue-like stenosis, and vascular remodeling of the unaffected pulmonary vessels. PTE or PEA is an operation that is curative for patients with CTEPH [2, 3].

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PTE is a technically demanding operation that is currently performed in a few select centers around the world. Proper patient selection, meticulous surgical technique, and careful postoperative management have contributed to the excellent outcomes of this operation [2–4]. A true endarterectomy (not an embolectomy) of all affected segments of the lung is essential to open up all affected areas of the pulmonary vasculature. The procedure, when performed successfully at an experienced center, significantly improves pulmonary hypertension, right ventricular dysfunction, tricuspid regurgitation, and limits retrograde expansion of thromboembolic material. It also improves perfusion of the ventilated lung, minimizing dead-space ventilation, and prevents arteriopathic changes in the remaining patent small pulmonary vessels. Here, we describe the surgical procedure as it is performed at the University of California San Diego (UCSD) Cardiovascular Institute. To date, UCSD has performed over 4000 PTEs, which is the largest volume of PTE surgeries in the world. It is this experience that forms the foundation of this chapter.

Indications

When the diagnosis of thromboembolic pulmonary hypertension has been confirmed, the decision for operation is made based on the severity of symptoms and the general condition of the patient. Early in the pulmonary endarterectomy experience, Moser and colleagues [5] pointed out that there were three major reasons for considering thromboendarterectomy: hemodynamic, alveolo-respiratory, and prophylactic. The hemodynamic goal is to prevent or ameliorate right ventricular compromise caused by pulmonary hypertension. The respiratory objective is to improve respiratory function by the removal of a large ventilated but unperfused physiologic dead space, regardless of the severity of pulmonary hypertension. The prophylactic goal is to prevent progressive right ventricular dysfunction or retrograde extension of the obstruction, which might result in further cardiorespiratory deterioration or death. Our subsequent experience has added another prophylactic goal: the prevention of secondary arteriopathic changes in the remaining patent vessels.

Most patients who undergo operation are within New York Heart Association (NYHA) Class III or Class IV. The ages of the patients in our series have ranged from 7 to 88 years. A typical patient will have a severely elevated pulmonary vascular resistance (PVR) level at rest, absence of significant comorbid disease unrelated to right heart failure, and the appearances of chronic thrombi on angiogram that appear to be relatively in balance with the measured PVR level. Exceptions to this general rule occur in symptomatic patients who exhibit pulmonary hypertension only with exercise.

Although most patients have a PVR level of less than 1000 dynes/s/cm^{-5} and pulmonary artery pressures less than systemic, the hypertrophy of the right ventricle that occurs over time makes pulmonary hypertension to suprasystemic levels possible. Therefore, many patients (approximately 20% in our practice) have a level of PVR in excess of 1000 dynes/s/cm^{-5} and suprasystemic pulmonary artery pressures. There is no upper limit of PVR level, pulmonary artery pressure, or degree of right ventricular dysfunction that excludes patients from operation, as long as there is evidence of thromboembolic disease that correlates with the degree of pulmonary hypertension.

There is a subgroup of patients who have a PVR level that is normal at rest, although elevated with minimal exercise. The condition is generally referred to as chronic thromboembolic disease or CTED. This is usually a young patient with significant thromboembolic disease and on occasion unilateral pulmonary artery occlusion with unacceptable exertional dyspnea because of an elevation in dead space ventilation. Operation in this circumstance is performed not only to re-perfuse lung tissue, but to reestablish a more normal ventilation perfusion relationship (thereby reducing minute ventilatory requirements during rest and exercise), and also to preserve the integrity of the contralateral circulation and prevent chronic arterial changes associated with long-term exposure to pulmonary hypertension. Inferior vena cava (IVC) filter insertion prior to surgery used to be routine in many centers. It has not been formally studied and has been abandoned by leading centers. IVC filter was not shown to increase long term survival [6].

Operation Principles

There are several guiding principles for the operation. Surgical treatment and endarterectomy must be bilateral because this is a bilateral disease in the vast majority of our patients. Typically, PTE is performed through a median sternotomy. The median sternotomy incision, apart from providing bilateral access, avoids entry into the pleural cavities, and allows the ready institution of cardiopulmonary bypass. More recently, a minimally invasive approach has been developed. This is a highly specialized operative technique that requires the combined skillset of an experienced minimally invasive surgeon, and an experienced PTE surgeon. This is not an approach for the novice surgeon. It involves cardiopulmonary bypass and circulatory arrest, with direct access to the pulmonary arteries via mini anterior thoracotomy incisions, without the use of a cross-clamp.

Cardiopulmonary bypass is essential to ensure cardiovascular stability when the operation is performed and to cool the patient to allow circulatory arrest. Excellent visibility is required, in a bloodless field, to define an adequate endarterectomy plane and to then follow the pulmonary endarterectomy specimen deep into the subsegmental vessels. Circulatory arrest is essential in these patients in order to create a bloodless field. These patients typically have copious bronchial blood flow, which can obscure the view of distal vessels in the absence of circulatory arrest. Again, there have been sporadic reports of the performance of this operation without circulatory arrest. However, it should be emphasized that although endarterectomy is possible without circulatory arrest, a complete endarterectomy is not. We always initiate the procedure without circulatory arrest, and a variable amount of dissection is possible before the circulation is stopped, but never complete dissection. The circulatory arrest periods are limited to 20 min, with restoration of flow between each arrest. With experience, the endarterectomy usually can be performed with a single period of circulatory arrest on each side. Circulatory arrest allows for a complete endarterectomy without increasing any potential risk of the procedure [7].

A true endarterectomy in the plane of the intima/media must be accomplished. It is essential to appreciate that the removal of visible thrombus is largely incidental to this operation. In most patients, no free thrombus is present; and on initial direct examination, the pulmonary vascular bed may appear normal. The early literature on this procedure indicates that thrombectomy was often performed without endarterectomy, and in these cases the pulmonary artery pressures did not improve, often with the resultant death of the patient.

Technical Aspects

The patient is laid supine on the operating table and appropriate monitoring lines, including a radial as well as a femoral arterial line, and a pulmonary artery catheter are placed. A transesophageal echocardiogram is also placed by the anesthesiologist. Brain activity is monitored by electroencephalogram, and a cooling jacket is placed around the head. The body's temperature is measured by use of bladder temperature, rectal temperature, as well as tympanic temperature. Then, once the patient is prepped and draped, a median sternotomy is made. It is important to ensure excellent hemostasis as these patients typically have enlarged and thin-walled venous collaterals and high CVP. In addition, having excellent hemostasis helps with the exposure and dissection of pulmonary vessels, which lie deep within the mediastinum. The pericardium is then incised longitudinally and attached to the wound edges. Full cardiopulmonary bypass is instituted with high ascending aortic cannulation and caval cannulae. The heart is emptied on bypass, and a temporary pulmonary artery vent is placed in the midline of the main pulmonary artery about 1 cm distal to the pulmonary valve.

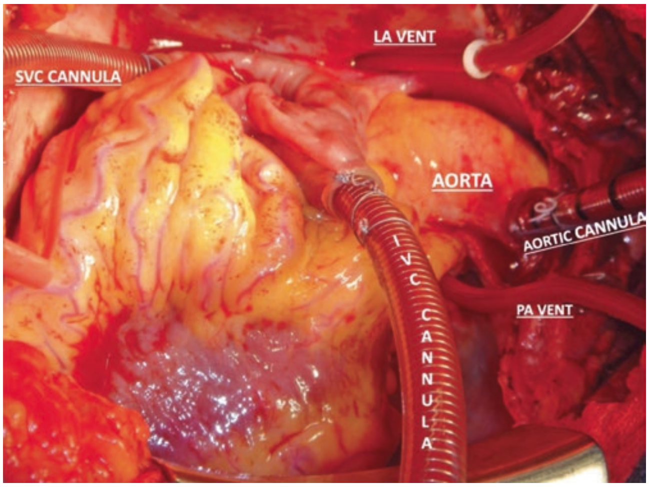

Fig. 78.1 Surgical field while the patient is cooling on cardiopulmonary bypass. The surgeon stands on the left side of the patient to start the endarterectomy of the right lung

The patient is then cooled to 20 °C with the pump oxygenator; surface cooling is performed with a cooling blanket as well as the head cooling jacket. Once ventricular fibrillation occurs, an additional vent is placed in the left atrium via the right superior pulmonary vein. Patients with CTEPH develop a large amount of bronchial collaterals, and as such it is important to ensure the left ventricle remains empty during the cooling process. Initially, it is most convenient for the primary surgeon to stand on the patient's left side and perform the endarterectomy on the right side (Fig. 78.1).

The surgeon then waits until body's core temperature has reached about 20 °C, as measured by both bladder and rectal temperatures. The approach to the right pulmonary artery is from the left side and it is usually medial, not lateral, to the superior vena cava. During the cooling period, some preliminary dissection can be performed, with full mobilization of the right pulmonary artery from the ascending aorta. The superior vena cava is also fully mobilized with a tourniquet applied circumferentially. Care is taken to avoid any injury to the phrenic nerve. Once the core temperature has reached 20 °C, an aortic cross-clamp is applied, and myocardial protection is provided through a single dose of antegrade DelNido cardioplegia (1 L). The entire procedure is now performed with a single aortic cross-clamp period with no further administration of cardioplegic solution. Additional myocardial protection is provided by using a cooling jacket, which surrounds the heart throughout the remainder of the procedure. Both tourniquets are now secured around the superior and inferior venae cavae to ensure complete drainage and to avoid any air entry in the venous cannulae during circulatory arrest. A modified cerebellar retractor, which has its tips filed, or a Madani PTE retractor is then used to expose the pulmonary artery between the aorta and the superior vena cava (Fig. 78.2).

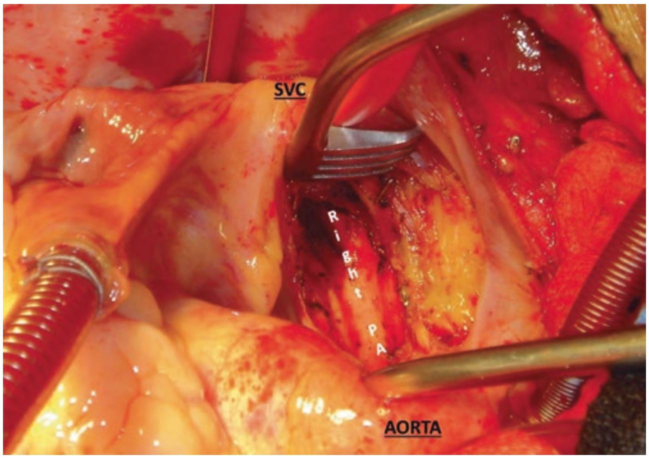

Fig. 78.2 Exposure of right pulmonary artery (PA)

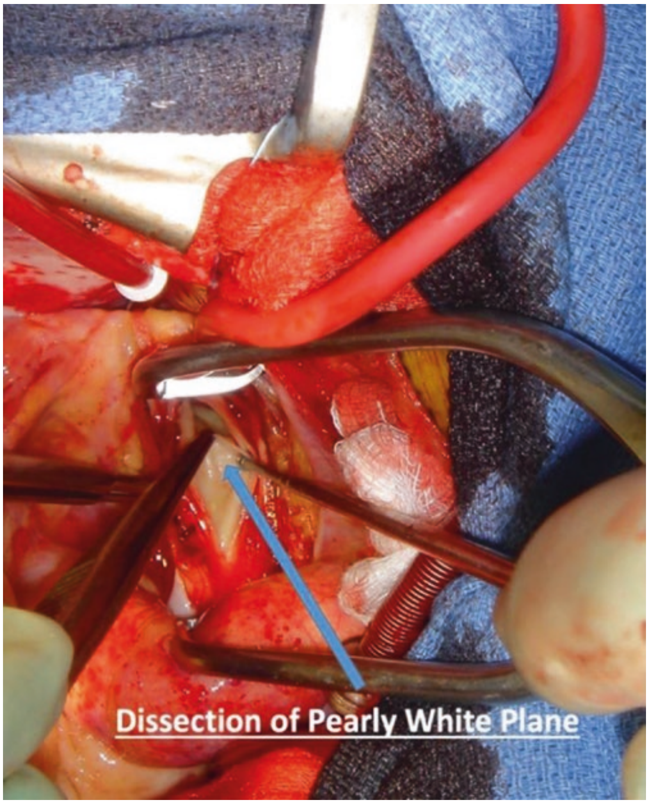

Fig. 78.3 Right pulmonary artery endarterectomy

An incision is made in the right pulmonary artery from beneath the ascending aorta out under the superior vena cava and entering the lower lobe branch of the pulmonary artery just after the takeoff of the middle lobe artery. It is important that the incision stays in the center of the vessel and continues in the middle of the descending pulmonary artery into the lower. Any loose thrombus, if present, is now removed. This is necessary to obtain good visualization. It is important to recognize, however, an embolectomy without subsequent endarterectomy is quite ineffective. Furthermore, in most patients with chronic thromboembolic hypertension, direct examination of the pulmonary vascular bed at operation generally shows no obvious embolic material. Occasionally the bronchial circulation and back-bleeding is not excessive, the endarterectomy plane may then be found during this early dissection. However, although a small amount of dissection can be performed before the initiation of circulatory arrest, it is unwise to proceed unless perfect visibility is obtained because the development of a correct plane is essential.

The correct plane appears pearly white (Fig. 78.3) which is smooth and silky in appearance and lies between the intima and media. A microtome knife is used to develop the endarterectomy plane posteriorly, because any inadvertent egress in this site could be repaired readily, or simply left alone. It is essential to identify the correct plane of dissection, which in most cases is between the intima and the media. A plane too deep will result in excessive thinning of the artery with the risk of tear in the distal branches, and a plane too shallow will result in incomplete endarterectomy.

The dissection is then carried out with the retractor in place. Circulatory arrest is then initiated, and the patient undergoes exsanguination into the reservoir. All monitoring lines to the patient are turned off to prevent aspiration of air. Snares are tightened around the cannulae in the superior and inferior venae cavae. It is rare to exceed a 20-min period for each side. The endarterectomy is then performed with an eversion technique. Because the vessel is everted and segmental and subsegmental branches are being worked on, a perforation here will become completely inaccessible and invisible later. This is why excellent visualization in an absolutely bloodless field provided by circulatory arrest is essential. It is important that each subsegmental branch is followed and freed individually until it ends in a “tail,” beyond which there is no further obstruction. Residual material should never be cut free; the entire specimen should “tail off” and come free spontaneously.

When only segmental and subsegmental disease is present, it is difficult to clearly visualize and perform a complete endarterectomy. In such distal cases, the plane of dissection is started more proximally in the normal plane of intima and/or occasionally media, and this plane of dissection is then carefully followed until the thickened fibrous tissue is reached. This technique can be quite challenging for the inexperienced surgeon as the remaining arterial tissue is quite thin and a tear through the arterial tissue is not inconsequential. A full endarterectomy is then completed in each of the segmental/subsegmental branches where disease is present. On occasion, circulatory arrest times of more than 20 min are required. In these situations, at about 20 min the circulation is restarted for about 10 min, at which time a second circulatory arrest is initiated, and the endarterectomy is completed. In most patients, the mixed venous oxygenation

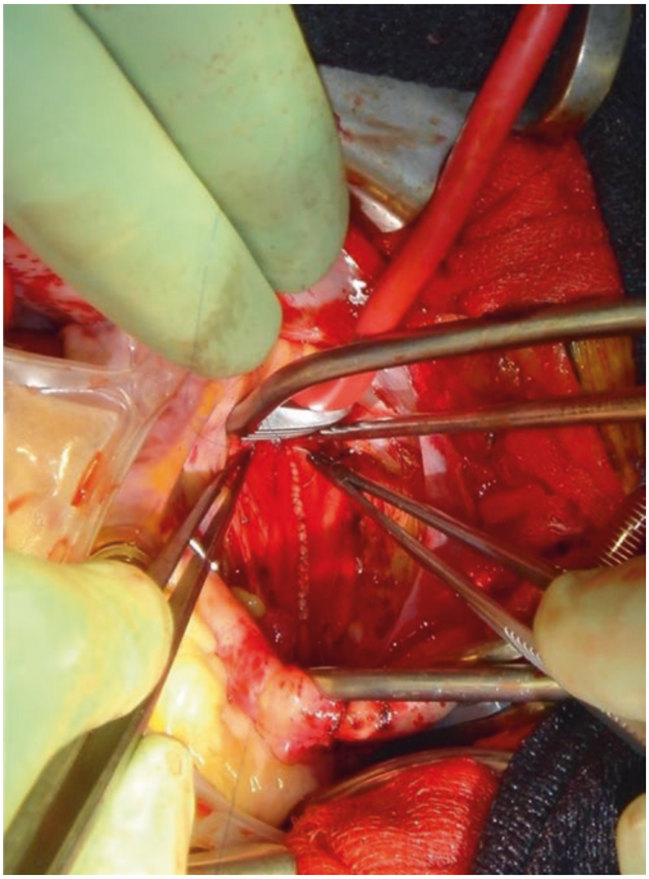

Fig. 78.4 Closure of right pulmonary artery

saturation is well above 90%, with 10 min of circulation. Once the right-sided endarterectomy is completed, circulation is restarted while maintaining a cold core body temperature. The pulmonary arteriotomy is then repaired with a continuous 6-0 polypropylene suture in a double-layer running fashion (Fig. 78.4).

After completion of the repair of the right arteriotomy, the surgeon moves to the patient's right side. The pulmonary vent catheter is withdrawn, and an arteriotomy is made similar to the right side and laterally to the pericardial reflection, avoiding entry into the left pleural space. Neither pleural cavity is entered. Care must be taken to avoid injury to the left phrenic nerve. Additional lateral dissection does not enhance intraluminal visibility, may endanger the left phrenic nerve, and makes subsequent repair of the left pulmonary artery more difficult. The heart, which remains wrapped within a cooling jacket, is now retracted using a mesh-like net retractor shown in (Fig. 78.5).

The left-sided dissection is virtually analogous in all respects to that accomplished on the right. The main obstructing material is a thickened scar-like tissue that obstructs each branch distally, and removal of only gross thrombus visible on initial inspection will be ineffective. The plane of dissection is developed posteriorly, and again the specimen is trimmed around the edges of the incision for subsequent closure. The duration of circulatory arrest intervals during the performance of the left-sided dissection is subject to the same restriction as the right. The specimen is followed in each segmental and subsegmental branch to ensure complete removal of the endarterectomy material.

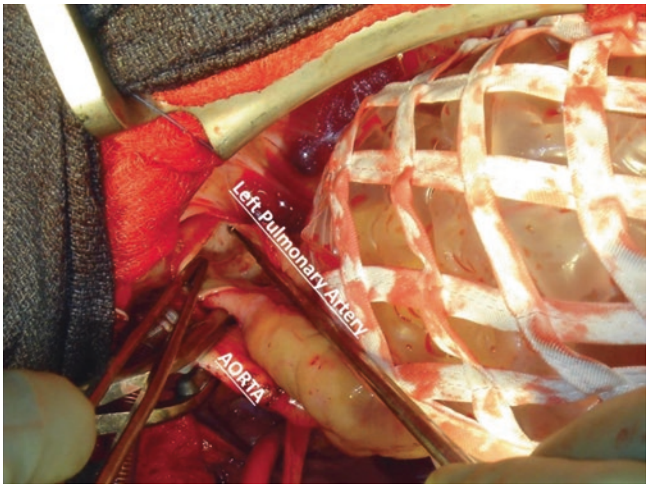

Fig. 78.5 Exposure of the left pulmonary artery

Whenever possible, the left lower lobe should be dissected circumferentially, and the specimen followed distally. The left main bronchus crosses anteriorly, and it is important to have firm grasp of the specimen at this location. If the specimen breaks, it is particularly difficult to regain exposure of these distal branches.

After completion of the endarterectomy, cardiopulmonary bypass is reinstituted, and warming is commenced. The rewarming period generally takes approximately 90–120 min but varies according to the body mass of the patient. Once the left pulmonary arteriotomy has been sutured closed, the heart is returned to its normal position. If other cardiac procedures are required, such as closure of patent foramen ovale/atrial septal defect (ASD), coronary artery bypass grafting, mitral, or aortic valve surgery, these are conveniently performed during the systemic rewarming period. The most common concomitant procedure is closure of foramen ovale or ASDs, followed by coronary bypass surgery.

Although tricuspid valve regurgitation is invariable in these patients and is often moderate to severe, tricuspid valve repair is not necessary unless there is an anatomic abnormality with the valve leaflets, chords, or overall structure. Tricuspid regurgitation secondary to annular dilation is typically left alone as right ventricular remodeling occurs within a few days, with the return of tricuspid competence. However, in cases with severe annular dilation, with annular measurement of over 4–4.5 cm, it may be advisable to proceed with tricuspid annuloplasty to prevent potential recurrence in the future. At the completion of all associated procedures, myocardial cooling is discontinued. The left atrial vent is removed, and the vent site is repaired. All air is removed from the heart, and the aortic cross-clamp is removed.

When the patient has fully rewarmed, cardiopulmonary bypass is discontinued. With a successful endarterectomy, the cardiac output is generally high, with a low systemic vascular resistance. Temporary atrial and ventricular epicardial pacing wires are placed. We typically use three 24 French soft mediastinal chest tubes, one of which is placed in the posterior pericardium as pericardial effusion posteriorly can occur. These drains are typically kept in place until drainage is below 200 cm^3/day and the patient is ambulatory. Wound closure is routine and similar to other cardiac procedures.

Figure 78.6 is surgical specimen removed from both lungs during pulmonary endarterectomy. The ruler measures 15 cm. Note that removal of proximal thromboembolic material without endarterectomy of all the distal branches would leave significant disease behind, without any relief in pulmonary pressures or the pulmonary vascular resistance. The specimen in Fig. 78.6 is characterized as level II disease on the right side and level III on the left side, according to the UCSD surgical classification.

There are four levels of pulmonary occlusive disease related to thrombus that can be appreciated, with level 0 (zero) symbolizing no evidence of chronic thromboembolic disease. Furthermore, the presence or absence of fresh thromboembolic material does not have any bearing on the classification. In other words, presence of stasis clot would no longer upgrade the surgical level of the disease. Table 78.1 summarizes the UCSD intra-operative classification.

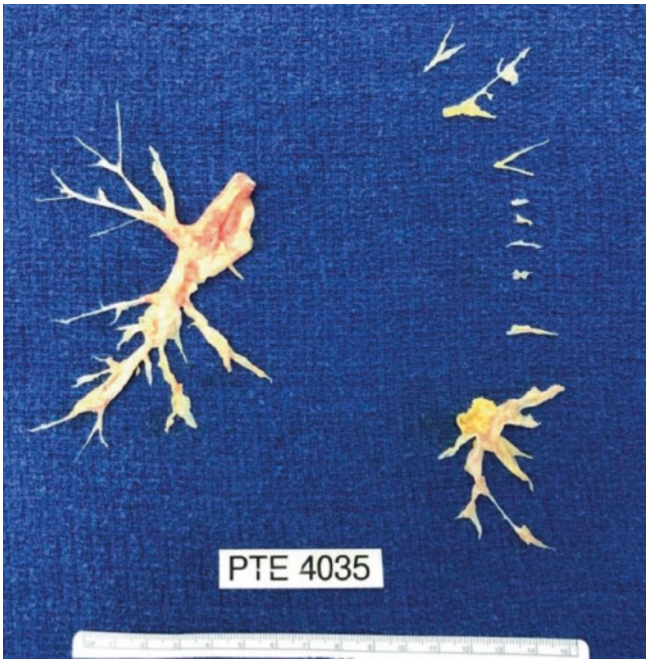

Fig. 78.6 Specimen removed from a patient indicating Level II disease on the right and Level III disease on the left

Table 78.1 UCSD CTEPH disease surgical classification

Level 0:	No evidence of chronic thromboembolic disease in either lung
Level I:	Chronic thromboembolic disease in the main pulmonary arteries
Level IC:	Complete occlusion of one main pulmonary artery with chronic thromboembolic disease
Level II:	Chronic thromboembolic disease starting at the level of lobar arteries, or in the main descending pulmonary arteries
Level III:	Chronic thromboembolic disease starting at the level of the segmental arteries
Level IV:	Chronic thromboembolic disease starting at the level of the subsegmental arteries

Postoperative care is similar to other cardiac procedures; and most patients are typically extubated within the first 48 h. The typical intensive care unit stay is about 2–3 days, and the average hospital stay is around 10–12 days. All patients undergo routine echocardiogram, V/Q scanning, as well as rest and exercise measurements of oxygen as a requirement prior to discharge. They will remain on lifelong anticoagulation using warfarin with a target international normalized ratio of about 3–4. Pulmonary endarterectomy can be curative for a vast majority of patients with excellent long-term outcomes. Our current 30-day and in-hospital and mortality rate is about 2% for all patients, and the current 10-year survival is about 75%. Most patients enjoy significantly improved hemodynamic numbers, and the majority will return to NYHA Class I/II functional level.

Surgical Advancements

With the advent of newly designed surgical instruments and retractor, we are now able to visualize distal pulmonary vasculature better and are able to remove disease that may be limited to only segmental and/or subsegmental vessels. By utilizing the techniques described above, we are now able to offer surgery to patients with distal disease, whom we may have turned down in the past. Figure 78.7 shows the surgical instruments used in PTE surgery at UC San Diego.

Also, more recently, the team at UCSD sought out to determine if a minimally invasive approach to PTE surgery was possible. Experiments were performed on multiple cadavers, which proved feasibility of performing a full endarterectomy into distal segmental and subsegmental arteries via mini anterior thoracotomy incisions, while providing adequate exposure. Using a preoperative computed tomography scan for surgical planning, the procedure is performed

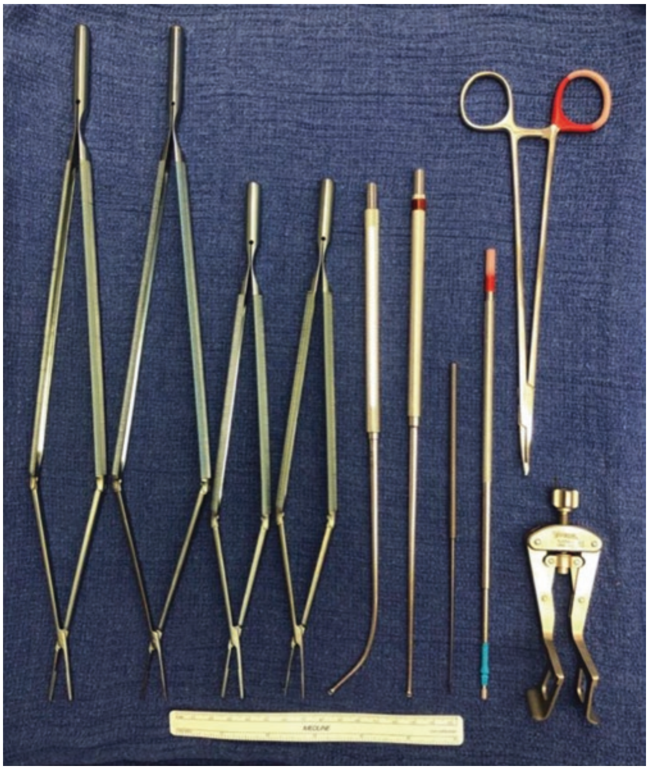

Fig. 78.7 Surgical instruments used during pulmonary thromboendarterectomy (PTE) surgery. From left to right, Madani double action PTE forceps, Jamieson suction/dissectors, microtome dissector, fine beaver blade, a "mini-peanut", and Madani PTE retractor

utilizing the second, or the third intercostal space through bilateral or unilateral mini anterior thoracotomies approximately 4–5 cm in length. The ideal location of the incisions is both high enough for central aortic cannulation, yet low enough for access to the pulmonary arteries. The arterial cannula is placed centrally in the ascending aorta, and venous cannulae in the femoral vein, right atrium and/or right internal jugular vein. For all patients, cardioplegia and cross-clamp were not used for purposes of simplification and to maximize space. An aortic root vent is intermittently utilized just prior to going back on cardiopulmonary bypass with each circulatory arrest. Pulmonary artery and left atrial vents are used. The usual protocol for circulatory arrest and exposure of the pulmonary arteries were used. Although in its infancy, with careful patient selection, and an expert surgeon, it is possible to perform a complete endarterectomy with visualization equivalent to that of a sternotomy. The minimally invasive approach to PTE surgery is not recommended for the novice PTE or minimally invasive cardiac surgeon.

The most important surgical advance has been redefining the limits of distal endarterectomy. In expert centers, PTE surgery can be successfully performed in patients with distal disease. This is attributed to advances in technology, instruments, and surgical experience. A new surgical classification has been developed to reflect the level of disease (i.e. lobar, segmental, subsegmental), as opposed to the type of disease. (UCSD classification Table 78.1). Depending on the level of experience of a center, operability may vary from center to center. A new definition of expert center has been proposed and evaluates the following; surgical mortality <5%, surgical volume >50 cases per year, and the ability to perform segmental endarterectomy, and the ability of the center to offer all treatment modalities (pulmonary thromboendarterectomy [PTE], balloon pulmonary angioplasty [BPA], medical therapy) [6].

Since the initial reports in 2012 from Japan, BPA has become an increasingly important tool in our armamentarium for patients who are not considered good surgical candidates. The results have varied from center to center and may not be generalizable, but they do show improved hemodynamic after multiple sessions of therapy. The long-term results and the effect of remaining disease within the pulmonary vasculature remains somewhat unknown. BPA should be reserved for expert centers, in patients who are not surgical candidates [6]. Figures 78.8 and 78.9 show the treatment algorithm proposed by the World Symposium on Pulmonary Hypertension and the treatment algorithm currently used at UC San Diego [8].

It is important to note that each treatment strategy affects different areas of the pulmonary vasculature. Clearly pulmonary hypertension directed medical therapy acts at the microvasculature level, and has very little effect on the obstructive disease as a result of thromboembolic occlusion. Both surgery and BPA address the obstructive disease, with

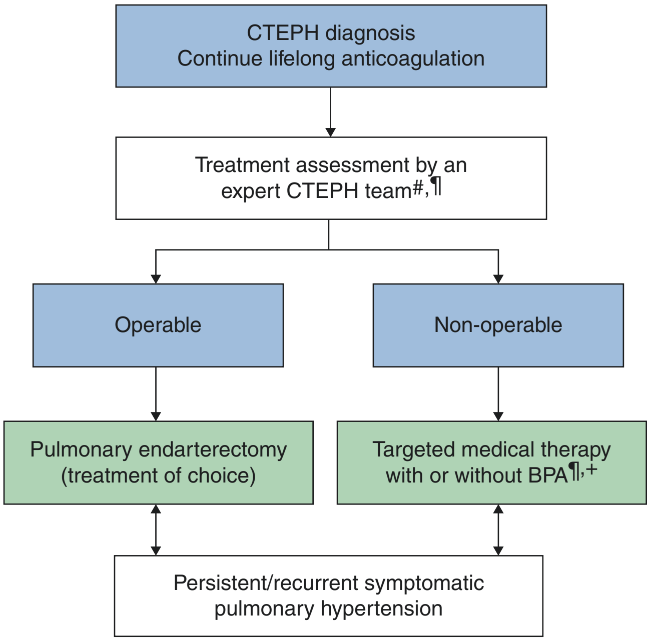
CTEPH diagnosis
Continue lifelong anticoagulation
Treatment assessment by an expert CTEPH team#,¶
Operable
Non-operable
Pulmonary endarterectomy (treatment of choice)
Targeted medical therapy with or without BPA¶,+
Persistent/recurrent symptomatic pulmonary hypertension

Fig. 78.8 Treatment algorithm proposed by the World Symposium on Pulmonary Hypertension [6]

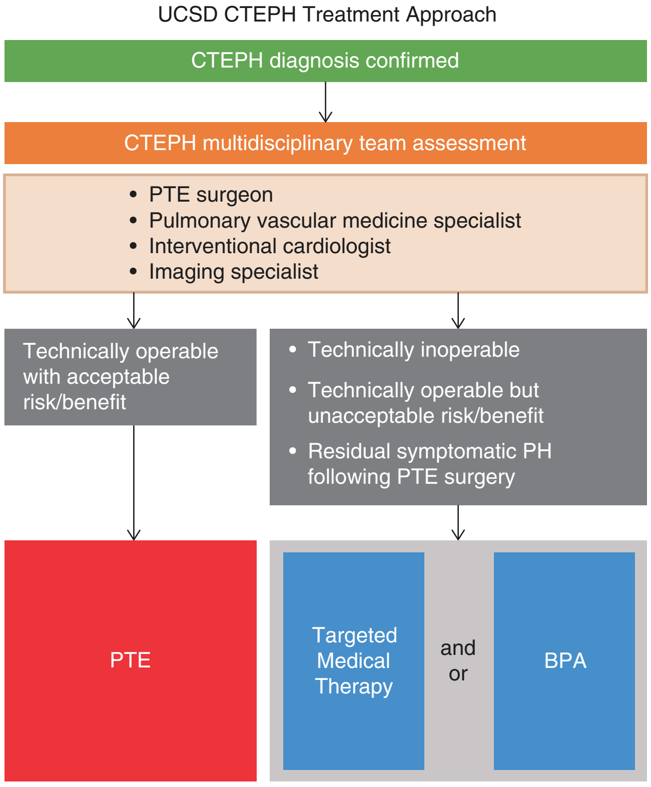
UCSD CTEPH Treatment Approach
CTEPH diagnosis confirmed
CTEPH multidisciplinary team assessment
• PTE surgeon
• Pulmonary vascular medicine specialist
• Interventional cardiologist
• Imaging specialist
Technically operable with acceptable risk/benefit
• Technically inoperable
• Technically operable but unacceptable risk/benefit
• Residual symptomatic PH following PTE surgery
PTE
Targeted Medical Therapy
and or
BPA

Fig. 78.9 Treatment algorithm used at UC San Diego for treatment of chronic thromboembolic pulmonary hypertension (CTEPH) [17]. *BPA* balloon pulmonary angioplasty, *PH* pulmonary hypertension, *PTE* pulmonary thromboendarterectomy

BPA generally addressing more distal disease at the subsegmental level and beyond. In experienced surgical hands disease starting at the segmental and even subsegmental level (Level III and IV), can be addressed and cleared. However, one can see how there may be a different treatment strategy at these distal levels depending on the center and the operators experience. Given the fact that the long-term results of BPA are unknown, and generally is a treatment that requires multiple sessions (generally 4–6 sessions), it should be reserved only for those patients who are not surgical candidates. Figure 78.10 is a cartoon indicating the different sites of action for each treatment strategy [8].

Results

More than 4000 pulmonary thromboendarterectomies have been performed at UCSD Medical Center since 1970. Most of these cases (over 3700) have been completed since 1990, when the surgical procedure was modified as described earlier in this chapter. The mean patient age in our group is about 51 years, with a range of 7–89 years. There is no gender difference. In nearly one-third of the cases, at least one additional cardiac procedure was performed at the time of operation. Most commonly, the adjunct procedure was closure of a persistent foramen ovale or atrial septal defect (26%) or coronary artery bypass grafting (8%) [2, 4].

A reduction in pulmonary pressures and resistance to normal levels and a corresponding improvement in pulmonary

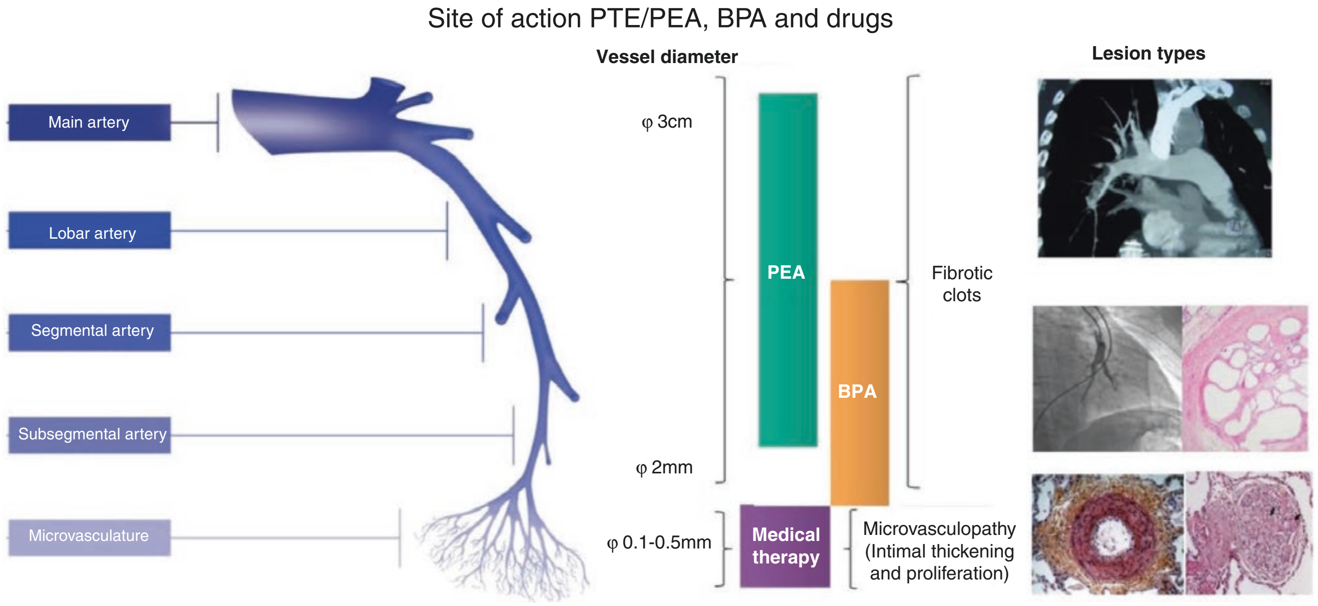
Site of action PTE/PEA, BPA and drugs
Vessel diameter
Lesion types
Main artery
Lobar artery
Segmental artery
Subsegmental artery
Microvasculature
φ 3cm
φ 2mm
φ 0.1-0.5mm
PEA
BPA
Medical therapy
Fibrotic clots
Microvasculopathy (Intimal thickening and proliferation)

Fig. 78.10 Site of action for pulmonary thromboendarterectomy/pulmonary endarterectomy (PTE/PEA) surgery, balloon pulmonary angioplasty (BPA), and pulmonary hypertension (PH) directed medical therapy. Please note possible crossover of PTE/PEA and BPA at around segmental/subsegmental level. An experienced surgeon can clear disease that starts at distal segmental/proximal subsegmental level (Level IV) [8]

blood flow and cardiac output are generally immediate and sustained [2, 4]. In general, these changes can be assumed to be permanent. Whereas before the operation, more than 95% of the patients are in NYHA functional Class III or IV; at 1 year after the operation, 95% of patients remain in NYHA functional Class I or II [4]. In addition, echocardiographic studies have demonstrated that with the elimination of chronic pressure overload, right ventricular geometry rapidly reverts toward normal. Right atrial and right ventricular enlargement regresses. Neurological complications from circulatory arrest appear to have been eliminated, probably as a result of the shorter circulatory arrest periods now experienced, and perioperative confusion and stroke are now no more frequent than with conventional open-heart surgery [4, 7]. Early postoperative hemorrhage required reexploration in 2.5% of patients, and only 40% of patients required intra- or postoperative blood transfusion. Despite the prolonged operation, wound infections are relatively infrequent.

Mortality Rate

Mortality rate is inversely related to the surgeon's and center's experience. Cannon et al. [9] were able to show a significant difference in mortality rate after the first 500 operations. The difference was maintained over long-term follow-up. In our own experience at UC San Diego, the mortality rate was 9.4% in 1989 and then it remained at about half ranging 4–5% for the more than 2000 patients who had undergone the operation since 1990 until 2010. Looking at our most recent experience over the last 10 years, the mortality rate has been about 1–2%. We also accept patients in whom we know that the entire degree of pulmonary hypertension cannot be explained by the occlusive disease detected by angiography but feel that they will benefit from the operation, albeit at higher risk. With the recent availability of new medical therapies, as well as BPA, those patients with significant residual pulmonary hypertension can benefit from such therapy [10].

Other Post-operative Complications

Although rare, patients undergoing pulmonary endarterectomy are subject to all complications associated with open heart and major lung surgery (arrhythmias, atelectasis, wound infection, pneumonia, mediastinal bleeding) but also may develop complications specific to this operation. These include persistent pulmonary hypertension, reperfusion pulmonary edema, and airway bleeding or massive hemoptysis.

A specific complication that occurs in most patients to some degree is localized pulmonary edema, or the "reperfusion response." Reperfusion pulmonary edema is defined as a radiologic opacity seen in the lungs within 72 h of pulmonary endarterectomy. This unfortunately loose definition may therefore encompass many causes, such as fluid overload and infection. The complication typically occurs within 24–72 h after surgery, but rarely it can manifest as late as 1 week following surgery [8, 11–17].

True reperfusion injury that directly adversely impacts the clinical course of the patient now occurs in approximately 10% of patients. In its most dramatic form, it occurs soon after operation (within a few hours) and is associated with profound desaturation. Edema-like fluid, sometimes with a pinkish bloody tinge, is suctioned from the endotracheal tube [8, 12]. Frank blood from the endotracheal tube, however, signifies a mechanical violation of the blood airway barrier that has occurred at operation and stems from a technical error, or occasionally may be related to bronchial collateral flow. This complication should be managed, if possible, by identification of the affected area by bronchoscopy and balloon occlusion of the affected lobe until coagulation can be normalized. In certain circumstances, when one lung ventilation is not possible, extra-corporeal support may be required.

Conclusion

It is increasingly apparent that pulmonary hypertension caused by chronic pulmonary embolism is a condition that is under-recognized and carries a poor prognosis without any treatment. Medical therapy is generally ineffective in prolonging life and only available for patients who are not surgical candidates. Currently, the only therapeutic alternative to pulmonary thromboendarterectomy in those who have been deemed inoperable by an expert center, is BPA and rarely lung transplantation. The advantages of thromboendarterectomy include a lower operative mortality and excellent long-term results without the risks associated with chronic immunosuppression and chronic allograft rejection. The mortality for thromboendarterectomy at our institution is now in the range of 2% with sustained benefit. These results are clearly superior to those for medical therapy or transplantation in both the short and the long term.

Although PTE is technically demanding for the surgeon and requires careful dissection of the pulmonary artery planes and the use of circulatory arrest, excellent short and long-term results can be achieved, as long it is performed at expert centers [9]. The successive improvements in operative technique developed over the last four decades now allow pulmonary endarterectomy to be offered to patients with an acceptable mortality rate and excellent anticipation of clinical improvement.

The primary problem remains that this is an under-recognized and under-treated condition. The likely incidence of CTEPH in the United States is at least 10 times the annual number of surgeries performed (approximately 400 per year). Increased awareness of both the prevalence of this condition and the possibility of a surgical cure should avail more patients of the opportunity for relief from this debilitating and ultimately fatal disease.

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Surgical Management of Atrial Fibrillation

79

Kareem Bedeir and Basel Ramlawi

High Yield Facts

- Goals of management of atrial fibrillation (AF) are hemodynamic optimization and stroke risk prevention. Both goals can be addressed medically, percutaneously or surgically.
- Duration of atrial fibrillation and size of atria predict the chances of successful cardioversion.
- CHADS-VASc score predicts stroke risk, and is the basis for indicated stroke risk reduction therapy or procedure.
- The left atrial appendage harbors 90% of clots formed in non-valvular atrial fibrillation.
- The majority of atrial fibrillation procedures include atrial lesions plus left atrial appendage exclusion. The latter may be isolated for stroke reduction purposes if rhythm control is not desired or possible.
- Atrial lesions can be achieved using cutting and sewing, radiofrequency ablation, cryoablation or other newer energy devices at various stages of development.
- Cox Maze III is regarded as the gold standard in AF surgery.
- Left atrial appendage exclusion can be achieved using sutures, staplers, clips, ties, luminal devices as well as other techniques in various stages of development.

Background

Atrial fibrillation (AF) significantly impacts quality of life, morbidity and mortality even with rate and/or rhythm control [1–3]. The most feared complications are related to systemic thrombo-embolism (STE), particularly stroke. Medically managed AF patients continue to have an elevated risk of stroke regardless of the attained rhythm [4, 5]. It is thus currently recommended that AF patients be offered anticoagulation based on their CHADS-VASc score, regardless of the rhythm attained [6]. Anti-arrhythmic drugs have suboptimal long-term success and carry multiple adverse effects and drug interactions. Anticoagulants, even the non-vitamin K antagonists, carry an elevated risk of bleeding that negatively impacts lifestyle, morbidity and mortality [7].

The limitation of medical management led to the development of procedures to address AF. Management of AF should address two problems: (1) Compromised cardiac output due to a fast rate and/or uncoordinated atrial kick, and (2) Elevated stroke risk due to stagnation within a fibrillating left atrium (LA).

Pathology

Atrial fibrillation requires a trigger and a substrate. A multitude of risk factors can trigger AF. Atrial overdistension (due to valvular, ventricular systolic and/or diastolic dysfunctions with their multiple etiologies) can trigger AF. Old age, hormonal and electrolyte abnormalities can also alter thresholds to trigger. For triggers to evolve into AF, a substrate is necessary. These are paths within the atrial myocardium that have a lower resistance to propagating a fast abnormal rhythm. The longer the substrates are subjected to the rhythm, the more resilient they get to cardioversion, and hence the concept "AF begets AF".

Electrophysiologists observed two broad anatomic locations important for procedural elimination of AF: (1) The myocardial sleeve transition zones which harbor a large majority of AF triggers. These include the junction of the four pulmonary veins with the LA, and the junctions of the superior vena cava (SVC) and coronary sinus (CS) with the right atrium. (2) The peri-atrial fat pad embedding

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the epicardial autonomic ganglia, most densely in the posterior wall of the LA and the ligament of Marshal. These ganglia have an exceedingly short refractory period together with an enhanced automaticity. These trigger zones locations together with common substrates are the basis for lesion sets designed to ablate AF.

Patients and Workup

The 2017 consensus statement from the Heart Rhythm Society and the European Heart Rhythm Association (HRS/EHRA) endorsed by the American College of Cardiology (ACC), the American Heart Association (AHA) and the Society of Thoracic Surgeons (STS) recommends a surgical or hybrid procedure to address AF in (1) all symptomatic patients undergoing other cardiac surgery, whether open (e.g. mitral surgery) or closed (e.g. coronary bypass), in (2) asymptomatic AF patients undergoing other cardiac surgery in an experienced center, and (3) as a stand-alone procedure in patients not undergoing other cardiac surgery, but are symptomatic and prefer a surgical approach, have failed or are not candidates for transcatheter ablation (TCA) [6].

Preoperative assessment includes electrolytes and thyroid function tests, a preoperative transthoracic echocardiogram (TTE) to assess for both LA thrombus as well as LA size. Increasing left atrial size has been correlated with failure of the procedure, although this is arguable [8]. All patients should undergo some assessment of their coronary circulation, whether a nuclear perfusion study, or our preference is to get a catheterization or a computerized axial tomographic angiography (CTA) to also assess for the circumflex anatomy in relation to the coronary sinus and LA isthmus lesion line. Patients with previous TCA should get a CT scan to evaluate for pulmonary vein stenosis. Electrophysiologic mapping is helpful to identify culprit triggers and pathways, especially before stand-alone AF procedures.

Procedures

Surgical procedures are largely for either rhythm control or for addressing the left atrial appendage (LAA), with the exception of the Corridor procedure [9, 10]. This procedure involves isolation of the sino-atrial node (SAN), a corridor of atrial tissue, and the atrio-ventricular node (AVN) from the remaining atrial tissue. Despite controlling the ventricular response rate, this failed to regain atrial synchrony, thus failed to address some hemodynamic and all the STE risks.

Surgical Rhythm Control

The Cox-Maze Procedures

The Maze procedure was introduced by James Cox in the early 1990s [11–14]. The Cox-Maze (CM) procedure interrupted substrates by creating a "Maze" through which impulse can migrate, activating the myocardium of both atria and eventually reaching the AVN as a coordinated signal. This was accomplished by cutting and sewing. The early procedure led to chronotropic incompetencies and unacceptable rates of permanent pacemaker implantations [15]. Serial modifications occurred eventually resulting in the CM-III, which soon became the gold standard for AF surgery [16]. Cox, and other groups, reported elimination of AF in up to 95% of patients after up to 10 years of follow-up [17–21]. Success rates were similar, whether an isolated CM-III or with a concomitant cardiac procedure [20]. The attained sinus rhythm also translated into a reduced stroke risk. In the 11.5 years follow-up of 306 patients by Cox and colleagues, only one minor stroke was reported in all patients over the follow-up period, despite 72% of patients not being anticoagulated [22]. Results regarding reduced stroke risk were however not consistently reproduced by others. The recommendation thus is that anticoagulation should not be solely discontinued based on the rhythm attained [6].

Drawbacks of the CM-III hindered its widespread adoption. It is a technically demanding operation. It requires a full sternotomy and an arrested heart. The cut-and-sew technique together with the empiric nature of the lesions added a significant amount to bypass and cross clamp times. Also exercise and stress-induced rhythm disturbances were reported, although these seemed to improve with time [23].

The advent of ablative energy devices simplified the operation by creating ablation lesions and replacing cutting and sewing. This utilized the same lesion set as the CM-III and was called the CM-IV (Fig. 79.1) [24–27]. Bipolar radiofrequency ablation (RFA) is better than unipolar RFA, with the former achieving consistent transmurality even when applied epicardially on a beating heart [25]. It however, cannot be safely applied around the mitral valve and the coronary sinus. Cryoablation is less deforming to the fibrous skeleton and is useful and effective near valve annuli and trigones. This should only be applied endocardially, because epicardial application, especially on a beating heart, lacks transmurality, and has the potential for thromboembolism (freezing left-sided blood without a cross clamp) [28].

The CM-IV allowed for a shorter and more simplified operation that can be more widely adopted. It also allowed for the possibility of a less invasive approach. It however maintained the need for an arrested heart, although right sided lesions can be done on beating heart. The CM-IV

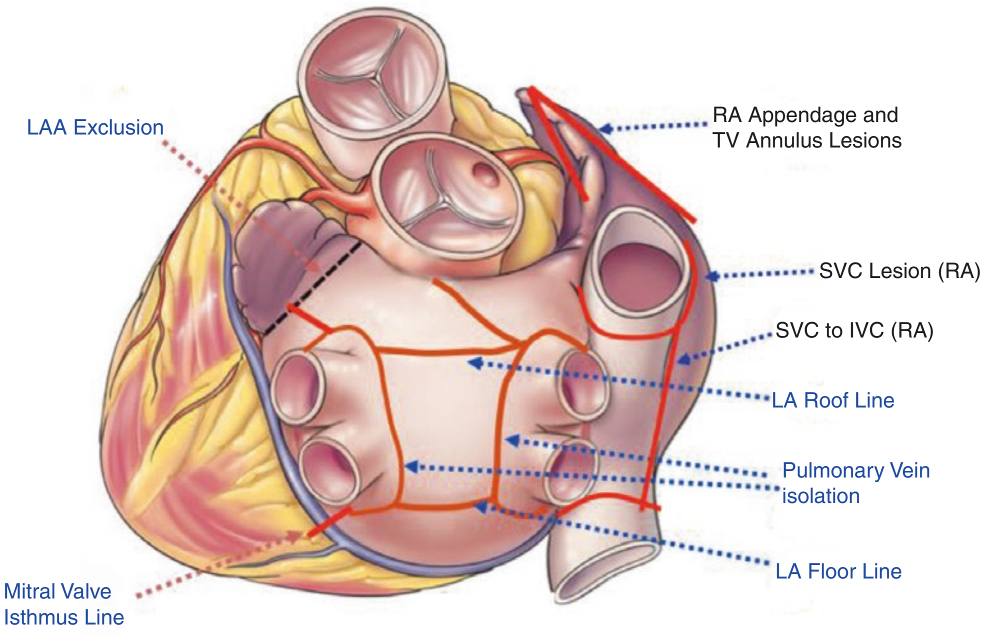

Fig. 79.1 Lesions for the Cox-Maze IV procedure. (With permission from Ramlawi B, Bedeir K. Surgical options in atrial fibrillation. J Thorac Dis 2015;7:204–13.)

showed good outcomes. It shortened operative time (cross clamp time for lone procedure: CM-III 93 min, versus CM-IV 41 min) while maintaining a comparable efficacy to the CM-III, for both lone and concomitant procedures [8, 29]. Reports of freedom from AF after the CM-IV reported rates of 89%, 93% and 89% at 3 months, 6 months and 12 months, respectively [8, 29]. Although these rates are apparently lower than those reported with the CM-III, patient population and outcome definitions were significantly different. The results of a propensity score matching comparison of CM-III to CM-IV did not show difference in the rate of AF elimination at 1 year [30].

Less Extensive Lesion Sets

The pulmonary veins were found to trigger the majority of AF signals [31]. The recognition of this fact together with the advent of ablative energy devices resulted in emergence of less extensive lesion sets for pulmonary vein isolation (PVI) that can be done on a beating heart without cardiopulmonary bypass. A simplified lesion set would also lend itself to an easier thoracoscopic less invasive operation.

Various lesion sets can achieve PVI. Authors have reported individual vein isolations, right and left isolations with or without connecting lines, box isolation of the posterior wall of the left atrium, or a combination of these with or without added LA lesion (isthmus or LAA lines). The literature demonstrates significant heterogeneity, making outcomes difficult to analyze, with inconsistent patient types, lesions sets, approaches used and outcome definitions. Studies thus report a wide range of freedom from AF and antiarrhythmic drugs at 1 year (from 20% to 88%) [32–36]. Gillinov and colleagues randomized 260 AF patients undergoing mitral valve surgery to ablation or no ablation, all using energy devices. The ablation group was further randomized to PVI versus a bi-atrial maze [37]. While ablation resulted in a higher degree of freedom from AF and anti-arrhythmic drugs (63% versus 29%), the difference between PVI and bi-atrial ablations did not reach statistical significance (66% with bi-atrial—47 patients, versus 61% with PVI—59 patients). A metanalysis that included 2260 patients undergoing surgical ablation reported similar survival rates biatrial or isolated left atrial lesion sets, however biatrial ablation led to a higher freedom from AF at all points during follow-up [38].

Pulmonary vein isolation however seems to be superior to TCA, at the expense of higher adverse events. The FAST trial randomized 124 patients with refractory AF to either minimally invasive PVI or TCA. Two-thirds of patients previously failed TCA. Pulmonary vein isolation led to a higher freedom from AF and anti-arrhythmic drugs at 1 year (66% versus 37%), but procedural adverse events were also significantly higher (34% versus 16%) [39].

Surgical ablations generally demonstrate a consistently higher rate of freedom from AF at 1 year, when compared to TCA [39, 40]. Surgery however also leads to higher rates of permanent pacemaker implantation [37, 39, 40]. We regard PVI as midway between the surgical maze and TCA in terms of efficacy. It is less efficacious than a maze yet simpler and can be done off-pump, and in a minimally invasive approach. It is more effective than TCA yet more invasive with a higher rate of pacemaker implantation.

The Hybrid Approach

The hybrid approach combines the transmurality and efficacy of the CM-IV's bi-atrial lesions while maintaining the advantages of minimally invasive off-pump approaches (epicardial PVI or endocardial TCA). This involves a minimally invasive epicardial off-pump approach, combined with a TCA. The procedure takes longer than either technique alone, and has been done either as a single or a staged operation [41, 42]. An advantage over either thoracoscopic PVI or TCA alone is better transmurality resulting in higher efficacy [43, 44]. Other advantage over thoracoscopic PVI is the availability of electrophysiologic mapping, allowing for a tailored, patient-specific lesion set. Advantages over TCA are better anatomical delineation with surgical exposure leading to less phrenic nerve or esophageal injury. Pericardial opening would also decrease the risk of effusions and cardiac tamponades. The Dual Epicardial and Endocardial Procedure (DEEP) pivotal trial (ClinicalTrials.gov identifier: NCT01661205) has recruited 220 patients for a hybrid procedure, and expected to report outcomes in the near future.

Left Atrial Appendage Exclusion

Patients with AF have a fivefold to 20-fold increased risk of stroke compared to the general population [45, 46]. Stopping anticoagulation safely based on cardioversion alone is backed by insufficient evidence. It is currently recommended that patients with successfully eliminated AF be still offered anticoagulation based on their CHADS-VASc score [6]. As mentioned earlier, anticoagulation in all forms has a significant impact on lifestyle, morbidity and mortality [7]. Also, 30% of AF patients requiring anticoagulation have relative or absolute contraindications to anticoagulation [47]. Among the remaining 70%, only 30% do actually take an anticoagulant for multiple reasons [47]. In addition, among those on warfarin, only 60% of patients are within therapeutic range [48, 49]. These rates demonstrate a serious limitation of anticoagulation in managing AF patients.

The LAA was found to harbor 90% of thrombi in nonvalvular AF, and 57% of thrombi in valvular AF [50]. This observation led to the theory that exclusion of the LAA from the circulation might decrease AF-related strokes, regardless of the rhythm. Ligation as well as excision of the LAA was attempted but results were inconsistent, largely due to significant rates of incomplete occlusion. Incompletely occluded LAAs led to a higher risk of thrombus formation than if not excluded at all [51–54]. The heterogeneity in techniques, completeness and outcomes made a correlation between LAA exclusion and stroke reduction difficult to make. The PROTECT-AF trial was a well powered RCT comparing anticoagulation to the percutaneous Watchman device for LAA exclusion [55]. Initial results showed higher procedural adverse event rate in the device group. The 45 months follow-up however demonstrated an equilibration in adverse events and an overall superior efficacy (from previously noninferior) with the device in stroke reduction compared to warfarin [56, 57]. The rate of embolic strokes in the device group was well below their CHADS-VASc-expected rate. This study is pivotal in proving the key nature of the LAA in AF-related strokes.

Surgical LAA exclusion is indicated in all AF patients undergoing concomitant cardiac surgery including thoracoscopic ablations. Due to the historically significant rate of incomplete occlusions, a multitude of devices have been developed for surgical LAA. Surgical devices require no initial period of anticoagulation, which is required for the percutaneous Watchman device. The absence of blood-device contact theoretically poses less risk of thrombosis, embolization or seeding by blood-borne infections. Also, some LAA morphologies not suitable for intraluminal occlusion would be more appropriate for epicardial surgical devices. This makes an isolated thoracoscopic LAA exclusion a consideration in cases with absolute contraindications to anticoagulation or unsuitable LAA morphology.

Surgical devices are developed with a goal to achieve the highest rate of complete occlusion with the lowest procedural adverse events. The two systems with the largest reported experiences are the Atriclip LAA exclusion system (Atricure Inc, Westchester, OH) and the Lariat suture delivery system (SentreHeart, Palo Alto, CA) (Fig. 79.2). Both systems can be utilized with concomitant cardiac surgeries or as a minimally invasive isolated procedure. The Lariat utilizes a combination of an epicardial tie, together with a percutaneous magnet-tipped catheter. The catheter is advanced into the LAA trans-septally, to magnetically attach to an epicardial guide wire. A radio-opaque tie is guided down the guidewire and tightened at the base of the appendage. Occlusion is reported to be complete in 89% at 1 year [58]. Both the European and US experiences report early concerns related to catheter-related myocardial injury necessitating further procedures, as well as high rate of pericarditis [58–60]. The Atriclip has become our preferred device for both open and thoracoscopic LAA exclusion. The clip consists of two parallel self-closing titanium tubes with nitinol springs, covered with braided polyester. The delivery system allows for repositioning and readjustment after initial deployment to ensure a perfect position. Reported rates of complete occlusion at 3 months were 98% and 100%, and no procedural complications were reported [61, 62].

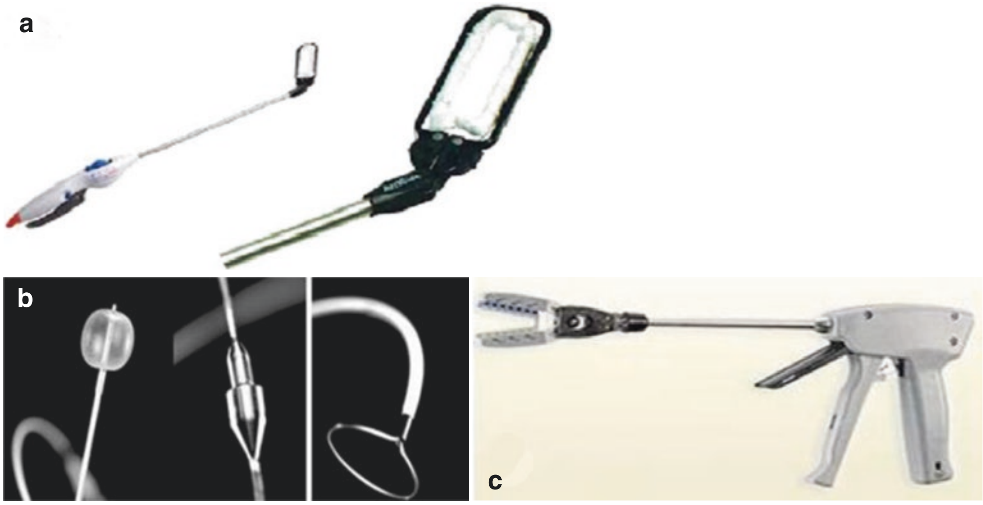

Fig. 79.2 Epicardial left atrial appendage exclusion devices A: Atriclip, B: Lariat, C: Tigerpaw. (With permission from Ramlawi B, Bedeir K. Surgical options in atrial fibrillation. J Thorac Dis 2015;7:204–13.)

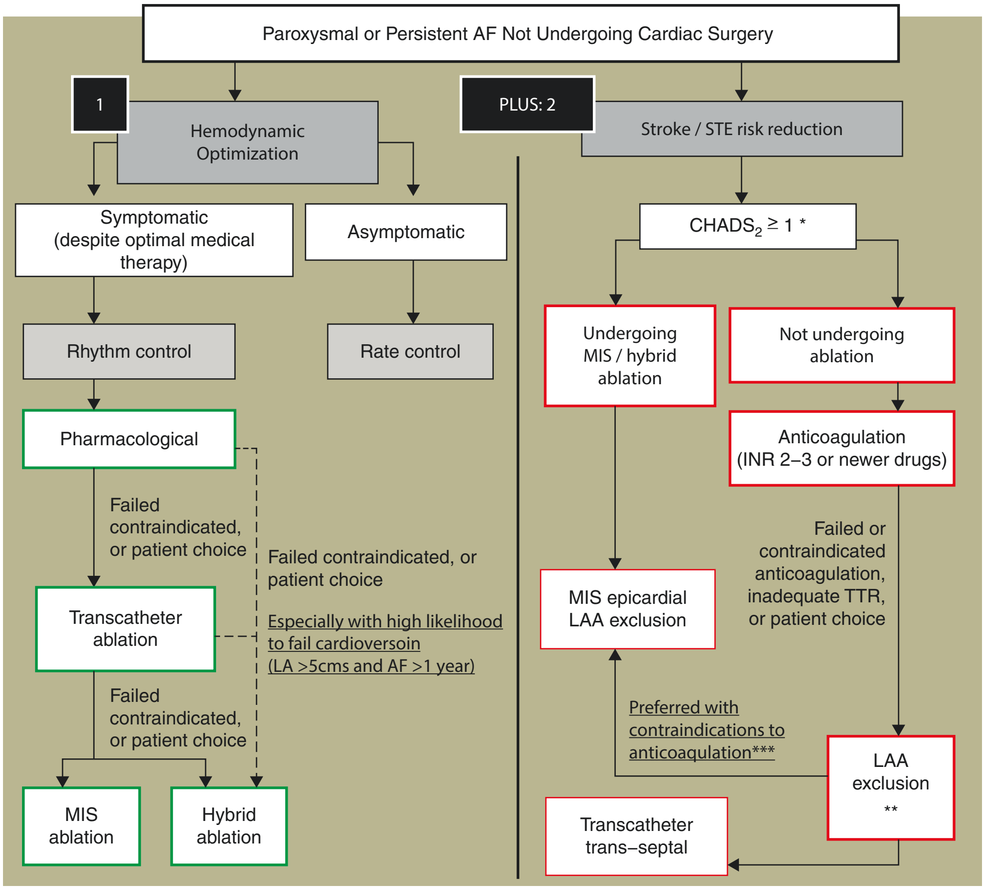
Paroxysmal or Persistent AF Not Undergoing Cardiac Surgery
1
Hemodynamic Optimization
PLUS: 2
Stroke / STE risk reduction
Symptomatic (despite optimal medical therapy)
Asymptomatic
CHADS$_2$ ≥ 1 *
Rhythm control
Rate control
Undergoing MIS / hybrid ablation
Not undergoing ablation
Pharmacological
Anticoagulation (INR 2–3 or newer drugs)
Failed contraindicated, or patient choice
Failed contraindicated, or patient choice
Especially with high likelihood to fail cardioversoin (LA >5cms and AF >1 year)
Failed or contraindicated anticoagulation, inadequate TTR, or patient choice
Transcatheter ablation
MIS epicardial LAA exclusion
Failed contraindicated, or patient choice
Preferred with contraindications to anticoagulation***
LAA exclusion **
MIS ablation
Hybrid ablation
Transcatheter trans–septal

Fig. 79.3 Simplified approach to the surgical management of atrial fibrillation patients not undergoing concomitant cardiac surgery. ∗: CHADS2 = 1 is controversial. The CHA2DS2VASc is also used. Renal failure is not included either system but is a risk factor for stroke in AF patients. ∗∗: Discontinuation of anticoagulation after LAA exclusion is reasonable if complete exclusion is confirmed at 3 months after surgery and/or patient is at high-risk for anticoagulation. ∗∗∗: MIS epicardial to LAA exclusion may be preferred in low surgical risk patients with no previous sternotomy or left thoracotomy. *AF* atrial fibrillation, *MIS* minimally invasive surgical, *STE* systemic thromboembolism, *LA* left atrial, *LAA* left atrial appendage, *INR* International normalized ratio, *TTR* time in therapeutic range. (With permission from Ramlawi B, Bedeir K. Surgical options in atrial fibrillation. J Thorac Dis 2015;7:204–13.)

Conclusion

Surgical management for AF is an exciting field with large potential for future growth. Studies comparing rate to rhythm control included only medically managed patients and their results cannot be applied to patients undergoing AF-related procedures. There is a good argument that effective surgical elimination of AF with LAA exclusion may be superior to medical management. Bi-atrial ablations are preferred, followed by isolated LA lesion sets, followed by TCA. The rate of pacemaker implantations is higher with surgical approaches than with TCA. The LAA should be addressed during ablation. The device that seems to have the highest rate of complete occlusion is the Atriclip. However each device has its advantages as well as its limitation. All patients with AF undergoing concomitant cardiac surgery should have ablations and LAA exclusions. In patients not undergoing concomitant cardiac surgery, our approach is summarized in Fig. 79.3.

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Hypertrophic Cardiomyopathy

80

Hao Cui and Hartzell V. Schaff

High Yield Facts

- Hypertrophic cardiomyopathy (HCM) is a primary myocardial disease characterized by left ventricular hypertrophy in the absence of other etiologies.
- HCM is an inherited disease with a prevalence estimated to be 1/500 for patients with phenotypic disease and 1/200 considering both genotype and phenotype positive patients.
- Asymmetric hypertrophy of left ventricle, especially the interventricular septum, is the hallmark of HCM.
- Approximately one third of symptomatic patients with HCM have resting left ventricular outflow tract (LVOT) obstruction (maximal subaortic pressure gradient ≥30 mmHg) and another third have a provokable LVOT obstruction.
- Consensus guidelines recommend initial medical therapy with β-blockers, verapamil, and/or disopyramide for patients with obstructive HCM.
- For those who remain symptomatic under optimal therapy or do not tolerate side effects of medication, invasive relief of LVOT obstruction should be considered.
- Transaortic septal myectomy is standard treatment for septal reduction, especially for patients with impaired functional capacity and a subaortic pressure gradient of more than 50 mmHg at rest or after provocation.
- Survival of patients following myectomy for obstructive HCM is similar to survival of HCM patients without obstruction and superior to survival of unoperated patients with obstructive HCM.

Introduction

Hypertrophic cardiomyopathy (HCM) is an inherited disease with a prevalence estimated to be 1/500 for patients with phenotypic disease and 1/200 considering both genotype and phenotype positive patients [1, 2]. Asymmetric hypertrophy of left ventricle, especially the interventricular septum, is the hallmark of HCM. Septal hypertrophy predisposes to systolic anterior motion (SAM) of the mitral leaflet, which causes left ventricular outflow tract (LVOT) obstruction and mitral regurgitation. Obstruction of the LVOT is considered to be present when the maximal subaortic pressure gradient is ≧30 mmHg. Approximately one third of symptomatic patients with HCM have resting LVOT obstruction and another third have a provokable LVOT obstruction [3].

Dynamic obstruction to outflow in HCM is associated with multiple exertional symptoms including dyspnea, chest pain, and syncope. In addition to its impact on quality of life, LVOT obstruction is also detrimental to late survival according to observational studies [4].

Consensus guidelines recommend initial medical therapy with β-blockers, verapamil, and/or disopyramide for patients with obstructive HCM [5, 6]. For those who remain symptomatic under optimal therapy or do not tolerate side effects of medication, invasive relief of LVOT obstruction should be considered. Transaortic septal myectomy is standard treatment for septal reduction, especially for patients with impaired functional capacity and a subaortic pressure gradient of more than 50 mmHg at rest or after provocation [5]. An observational study suggests that survival of patients following myectomy for obstructive HCM is similar to survival of HCM patients without obstruction and superior to survival of unoperated patients with obstructive HCM [7]. The beneficial effect of septal myectomy on late survival is supported by other studies showing reduced incidence of implantable cardioverter defibrillator (ICD) discharges [8], diminished mitral regurgitation [9], improved pulmonary hypertension [10] and some degree of reversed myocardial remodeling [11] in patients following myectomy.

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In addition to subaortic myectomy for typical obstructive HCM, operation is possible in other subsets of HCM patients. In patients with midventricular obstruction there is obstruction to ejection of blood due to contact of the septum with the papillary muscles. With pure midventricular obstruction, the mitral valve (MV) leaflets do not contribute to obstruction, and there is no SAM. Midventricular obstruction leads to a high intraventricular pressure in the apical area, and this high pressure in combination with subendocardial ischemia predisposes to apical aneurysms [12, 13]. For these patients, septal myectomy is usually performed through an apical incision. Based on different anatomical variants, isolated transaortic approach or combined transaortic plus transapical approaches can be used to adequately relieve the obstruction [14–16]. Both procedures provide good immediate relief of exertional symptoms and excellent long-term outcomes.

Surgical treatment is also possible for patients with nonobstructive HCM when there is ventricular hypertrophy that reduces left ventricular diastolic filling. Although most patients with apical HCM are asymptomatic, some may suffer severe diastolic dysfunction due to a very small ventricular cavity. Apical myectomy aiming to enlarge the ventricular volume can improve hemodynamics and functional capacity and may eliminate or delay the need for cardiac transplantation [17].

Contraindications to myectomy in patients with HCM are similar to contraindications to other types of cardiac surgery such as advanced age and frailty and concomitant illnesses that limit expected survival. In patients with obstructive HCM and surgical contraindications, alcohol septal ablation may be a useful alternative choice for septal reduction [5, 18].

Surgical Treatment

Preoperative Evaluation

For patients undergoing surgical treatment, transthoracic echocardiography (TTE) is the most commonly used imaging technique. Left ventricular morphology, especially the subaortic area, can be assessed, and hemodynamics can be documented by Doppler study. Moreover, TTE can identify systolic anterior motion of the MV leaflets, an important element in LVOT obstruction, as well as presence or absence of intrinsic MV disease and anomalies of the mitral apparatus that may contribute to LV outflow tract obstruction or mitral regurgitation.

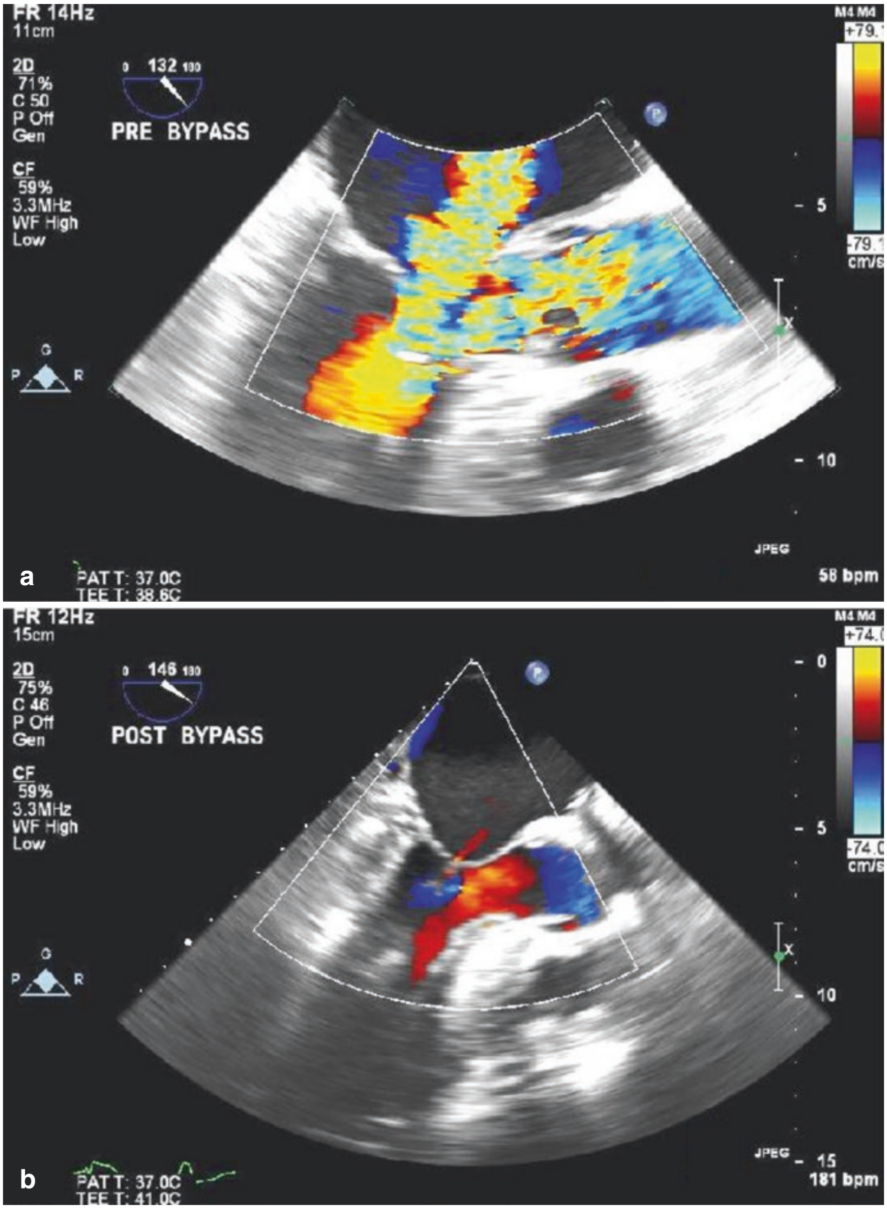
Identification of intrinsic MV disease (leaflet prolapse or calcific stenosis) is important because MV repair will be necessary at the time of myectomy [19, 20]. For most patients with obstructive HCM and mitral regurgitation in whom no intrinsic MV disease is identified preoperatively, we favor proceeding with septal myectomy to relieve obstruction and SAM, and then re-examining the MV on the postbypass transesophageal echocardiogram (TEE). It has been our experience that adequate septal myectomy reduces or eliminates SAM-mediated mitral regurgitation in over 95% of patients [9]. Although a posteriorly directed jet of regurgitation is said to be associated with SAM-mediated mitral regurgitation, we have observed attenuation or elimination of central mitral regurgitation after septal myectomy (Fig. 80.1). If direct MV surgery is required, we always attempt repair rather than defaulting to prosthetic replacement as follow-up demonstrates better outcome of patients having septal myectomy and MV repair compared to those having myectomy and MV replacement (Fig. 80.2) [9].

It is important to detect latent obstruction in symptomatic patients with HCM who have no or minimal LVOT gradients when sedentary [21]. These patients may present with typical symptoms of exertional dyspnea, angina, and/or syncope with minimal hemodynamic abnormality at rest. During clinical evaluation, provocative methods such as the Valsalva maneuver, inhalation of amyl nitrite, or simple exercise may be used to elicit the murmur of outflow obstruction. Latent obstruction is confirmed using these maneuvers during Doppler echocardiography. If labile outflow tract obstruction is strongly suspected but not confirmed by Doppler echocardiography, hemodynamic cardiac catheterization is performed with isoproterenol stimulation (Fig. 80.3) [22]. Other provocative techniques include infusing nitrates and/or eliciting premature ventricular contraction (PVC) [23]. In general, documentation of an LVOT gradient of 50 mmHg or more by one of these methods is evidence that obstruction may be the cause of limiting symptoms and that myectomy should be considered in patients who do not respond to medical therapy (Fig. 80.4).

Subaortic septal thickness should be reviewed for planning operation, but in our view, length of the enlarged septum is more important the subaortic septal thickness. Some surgeons have cautioned against transaortic myectomy in patients with septal thickness <18 mm because of concern regarding iatrogenic ventricular septal defect and/or inadequate gradient relief [24, 25]. We have not used degree of subaortic septal hypertrophy as a contraindication for septal myectomy; indeed approximately one third of our patients

Fig. 80.2 Outcome of mitral valve procedures with myectomy in patients with hypertrophic cardiomyopathy. Overall survival of patients following concomitant mitral valve surgery and myectomy was similar to survival of the age- and sex-matched general U.S. population. As seen in the right panel patients with myectomy and mitral valve repair had better survival than patients with myectomy and valve replacement. *MV* mitral valve, *MVS* mitral valve surgery. (Reproduced from Hong et al. [9] with permission of the publisher. Copyright ©2016, Elsevier)

Fig. 80.1 Panel (**a**) shows prebypass transesophageal Doppler echocardiogram demonstrating severe centrally directed mitral regurgitation. Panel (**b**) shows trivial central mitral regurgitation following isolated transaortic myectomy. (Reproduced from Hang et al. J Am Soc Echocardiogr. 2019;32(3):333–40)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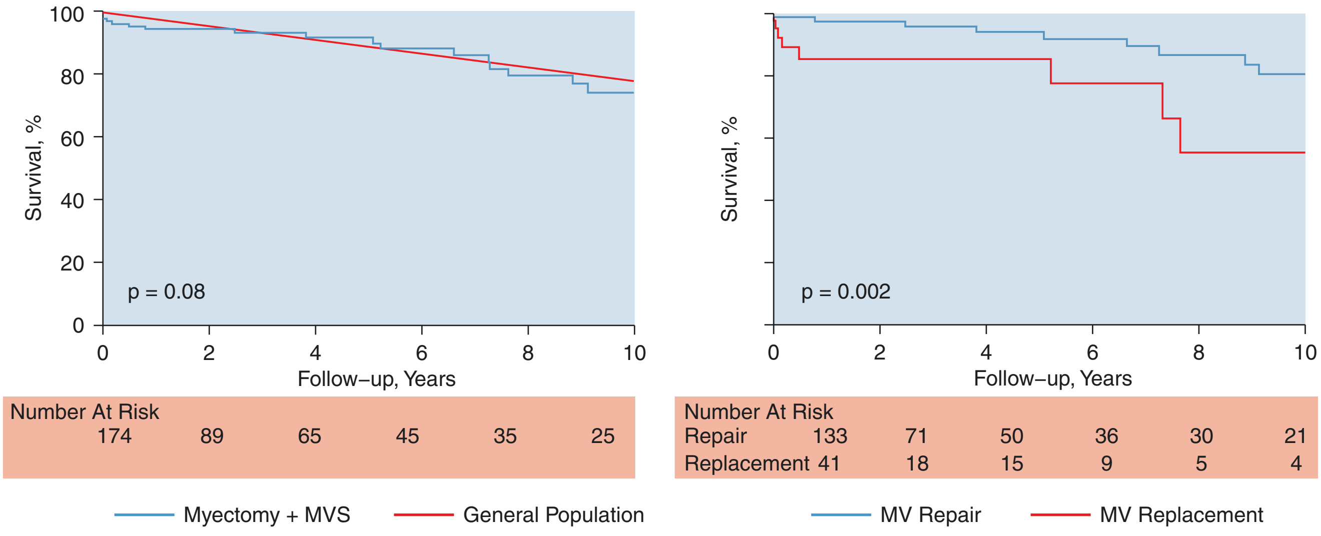


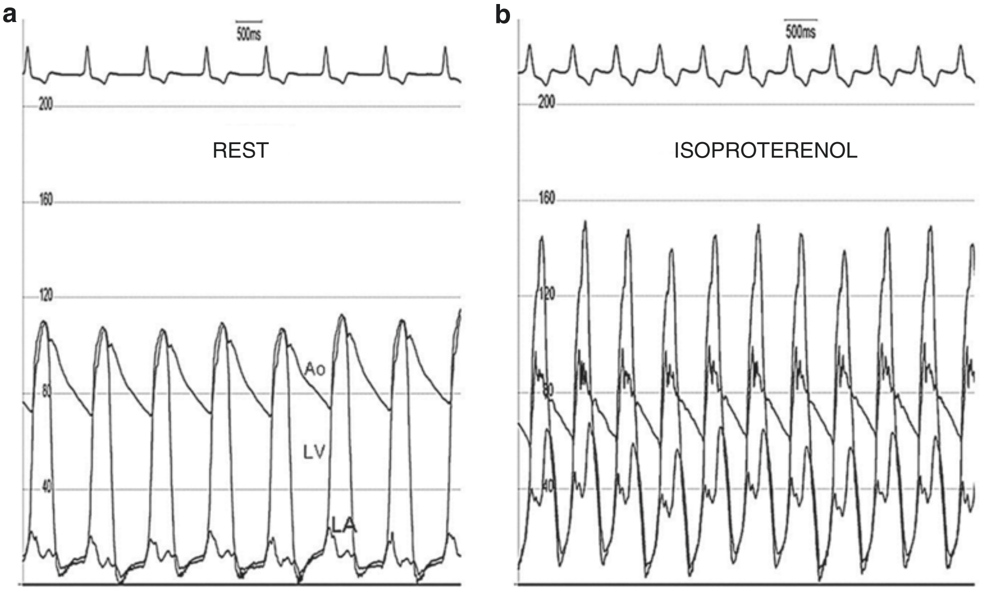


Fig. 80.3 (**a**) Left atrial (LA), left ventricular (LV), and aortic (Ao) pressures at baseline and (**b**) after maximal isoproterenol infusion of a representative patient. (Reproduced from Elesber et al. [22] with permission of the publisher. Copyright ©2008, Elsevier)

undergoing transaortic myectomy have septal thickness of 18 mm or less (Figs. 80.5 and 80.6) [26].

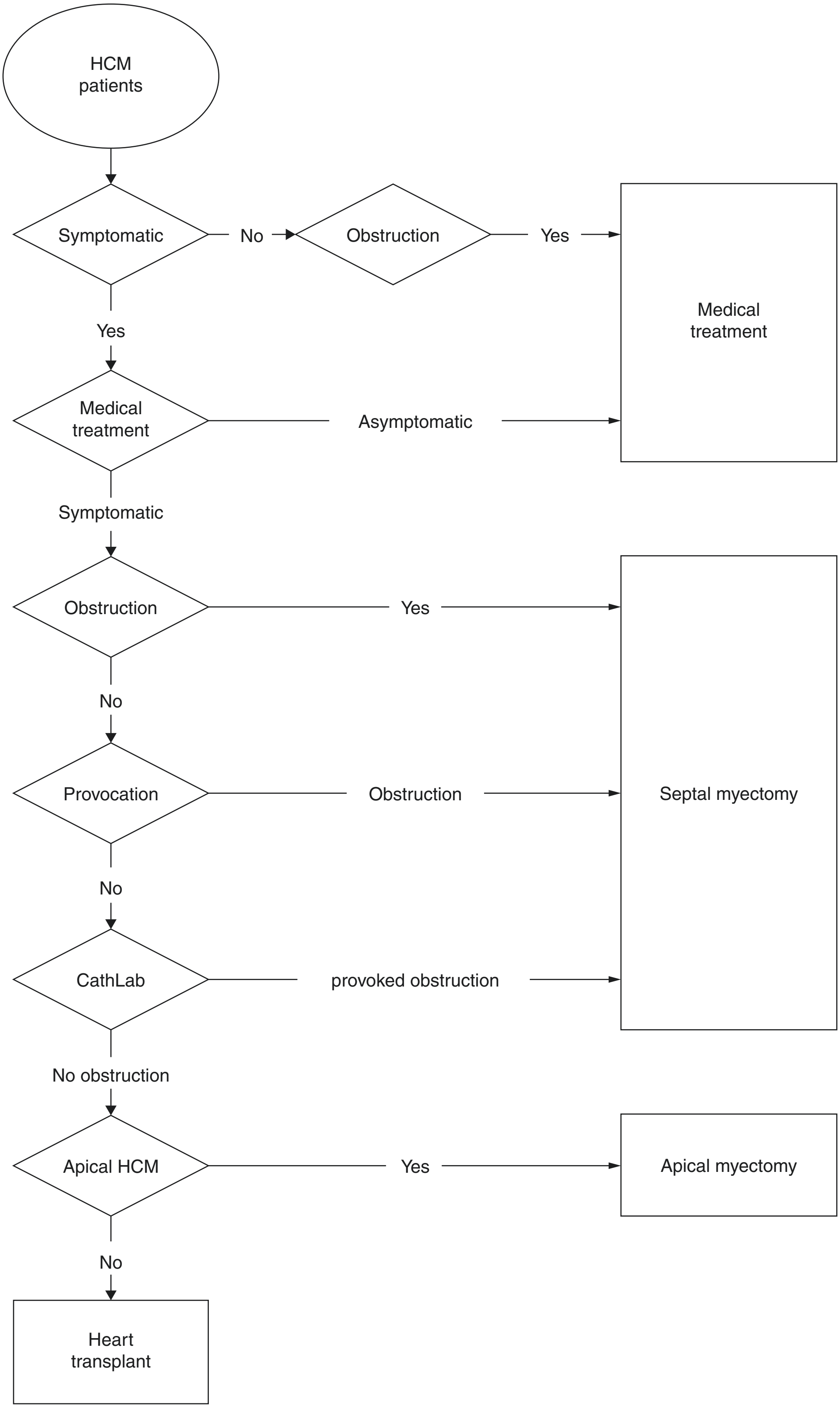
Cardiac magnetic resonance (CMR) is not used routinely in surgical planning for most patients with subaortic obstruction, but additional information is obtained with contrast-enhancement. Late gadolinium enhancement (LGE) appears to be an in vivo marker of myocardial fibrosis, and extent of LGE may be useful in risk prediction models for sudden cardiac death (SCD); LGE also appears to correlate with progression to end-stage HCM with systolic dysfunction [27]. Imaging with CMR is used routinely during surgical evaluation of patients with apical HCM to visualize LV morphology and to quantify LV volume. Candidates for apical myectomy to enlarge the left ventricular cavity typically have an LV end-diastolic volume <50 mL/m^2 and LV stroke volume <30 mL/m^2, although these indices are age- and sex-specific, and should be evaluated on an individual basis [28].

Electrophysiological evaluation is important in preoperative assessment of HCM patients. Approximately 40% of the patients develop left bundle branch block after septal myectomy, and presence of right bundle branch block preoperatively greatly increases the risk of complete heart block after operation [29]. In our experience in over 2500 patients having septal myectomy, complete heart block requiring a pacemaker occurred in 34% of those who had right bundle branch block on resting preoperative electrocardiogram compared to a risk of <1% for patients with normal sinus rhythm and no conduction abnormalities before surgery. The increased risk of complete heart block following myectomy can be reduced by moving the initial incision in the septum slightly anteriorly to spare the posterior fascicular of the left bundle branch.

Atrial fibrillation (AF) is the most common arrhythmia in patients with obstructive HCM, and often patients are very symptomatic with fatigue and lightheadedness during the arrhythmia. In patients who have symptoms suggestive of AF, preoperative electrophysiological assessment with Holter monitoring is helpful both for diagnosis of atrial arrhythmias and possible ventricular arrhythmias which may signal the need for an ICD to prevent sudden cardiac death. Frequently, symptoms associated with AF are better tolerated after outflow tract obstruction has been relieved. Nevertheless, concomitant surgical ablation at the time of myectomy should be considered in all patients with chronic AF and those with debilitating symptoms associated with episodes of paroxysmal arrhythmia. In recent reports, surgical ablation of AF with myectomy appears to be effective in reducing late AF and maintaining sinus rhythm in 70–80% of patients [30, 31].

Exertional chest pain or pressure is a common presentation in patients with HCM, especially obstructive HCM. We obtain coronary angiography preoperatively in patients with angina to confirm the presence or absence of occlusive coronary artery disease (CAD) and to exclude myocardial bridging. In the absence of ischemic symptoms, assessment of the coronary arteries is indicated in patients at increased risk of atherosclerosis. In a study by Thalji et al. probability of CAD was 10% or less for men aged 52 years or younger and for women aged 66 years or younger (Fig. 80.7) [32]. Although coronary CT angiography can detect coronary calcification, focal stenosis, and myocardial bridging, angiography is preferred for surgical planning in most patients. Unroofing can be performed for myocardial bridging in proper candidates (Fig. 80.8) [33].

Fig. 80.4 Flowchart illustrating preoperative evaluation of latent obstruction in patients with hypertrophic cardiomyopathy


HCM patients
Symptomatic
No
Obstruction
Yes
Medical treatment
Yes
Medical treatment
Asymptomatic
Symptomatic
Obstruction
Yes
No
Provocation
Obstruction
Septal myectomy
No
CathLab
provoked obstruction
No obstruction
Apical HCM
Yes
Apical myectomy
No
Heart transplant

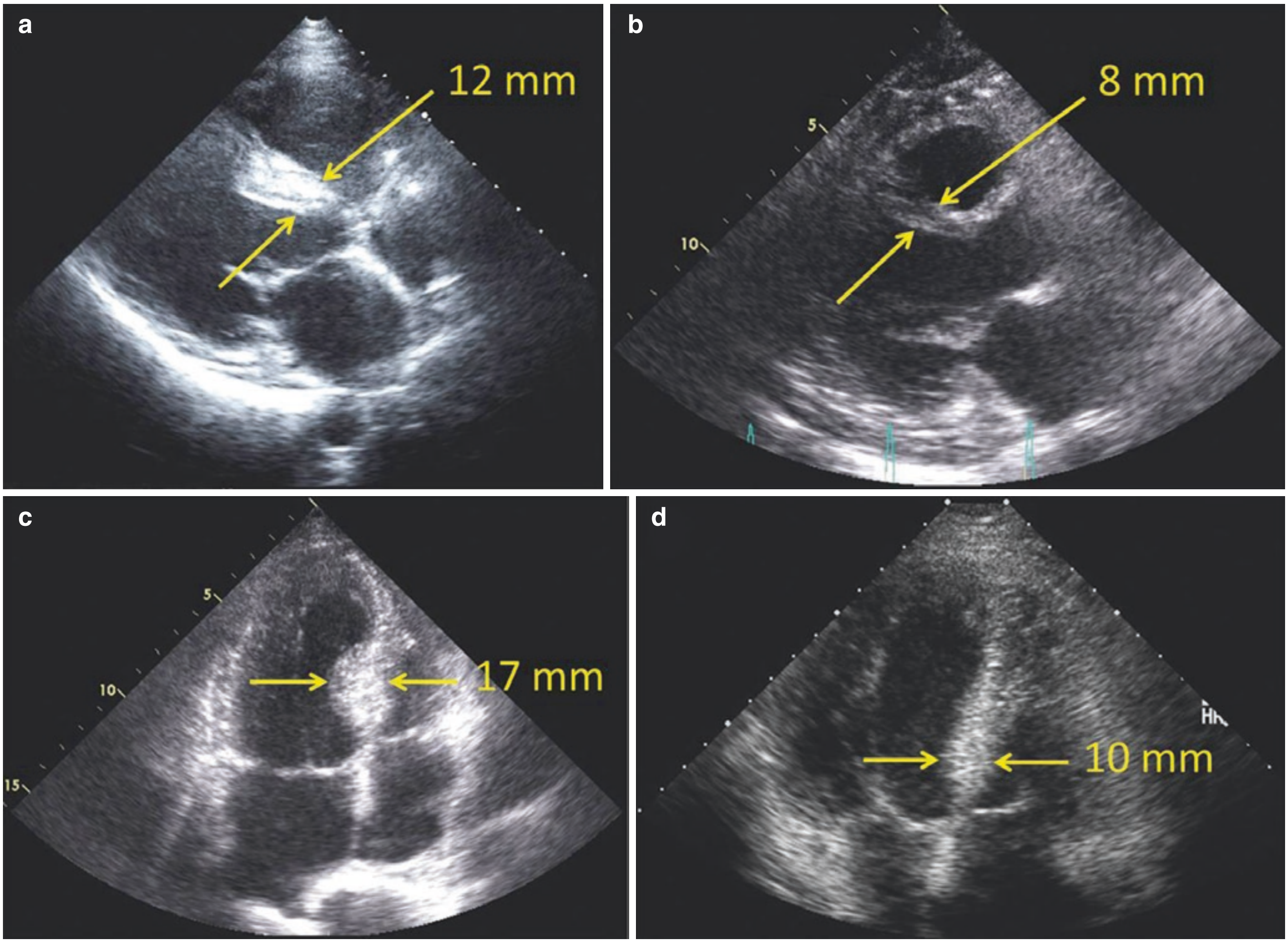
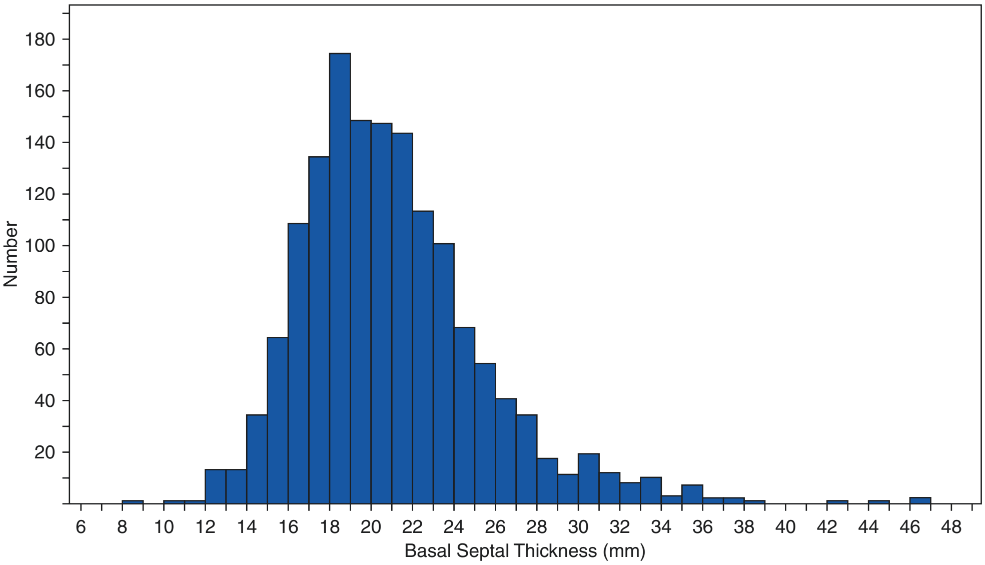


Fig. 80.5 Panels (**a**) and (**b**) show preoperative and postoperative long-axis images from transthoracic echocardiography. Before myectomy, basal septal thickness measured 12 mm and this was reduce to 8 mm postmyectomy. Preoperative and postoperative 4-chamber images from another patient are shown in panels (**c**) and (**d**). In this patient the pre-myectomy basal septal thickness was 17 mm which was reduced to 10 mm postoperatively. (Reproduced from Nguyen et al. [26] with permission of the publisher. Copyright ©2017, Oxford University Press)

Fig. 80.6 Histogram showing distribution of basal septal thickness among 1486 patients undergoing transaortic septal myectomy at Mayo Clinic. (Reproduced from Nguyen et al. [26] with permission of the publisher. Copyright ©2017, Oxford University Press)



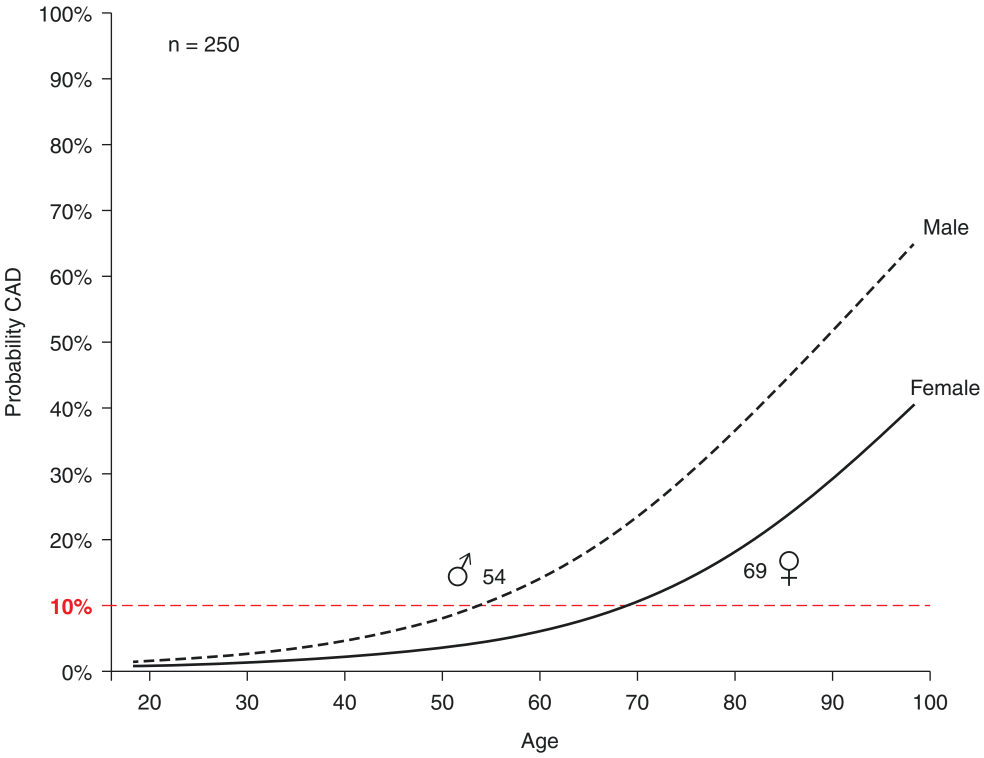


Fig. 80.7 Age thresholds consistent with a 10% or less predicted probability of coronary artery disease in men and women free of diabetes and peripheral vascular disease undergoing septal myectomy. (Reproduced from Thalji et al. [32] with permission of the publisher. Copyright ©2013, Elsevier)

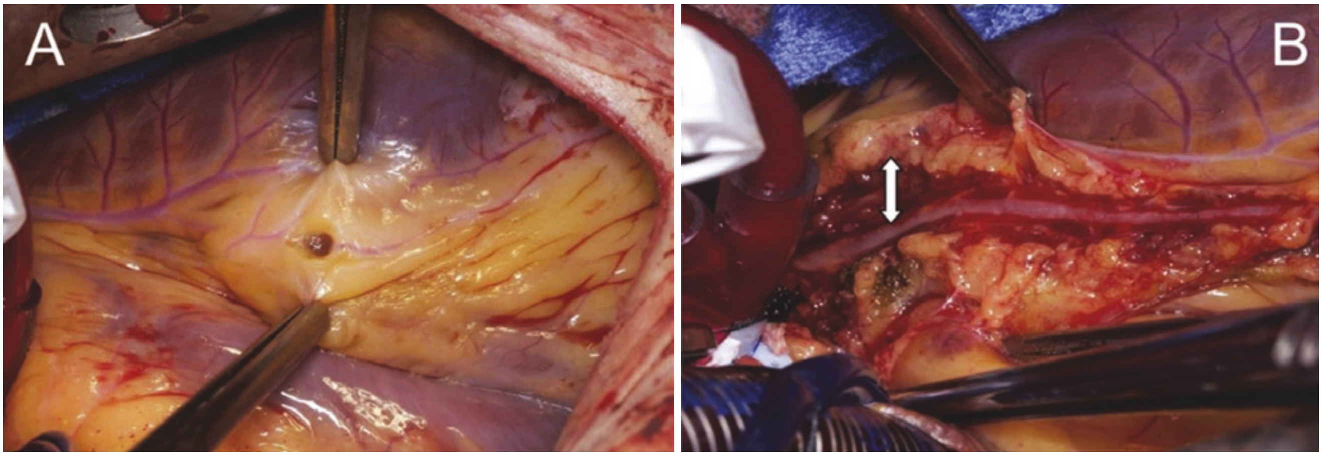


Fig. 80.8 (**a**) Bridged segment of left anterior descending artery, approximately 40 mm in length. (**b**) Bridged segment of left anterior descending artery now unroofed. The double arrow shows the thickness of muscle that was overlying the left anterior descending artery. (Reproduced from Kunkala et al. [33] with permission of the publisher. Copyright ©2014, Elsevier)

Operative Methods

After induction of general anesthesia and placement of routine monitoring lines, the patient is evaluated with TEE to confirm the cardiac anatomy with particular attention to MV function and appearance of the ventricular septum. The operation is initiated with median sternotomy, and normothermic cardiopulmonary bypass is established with central aortic cannulation and a single, two-stage venous return cannula. After placing the aortic inflow cannula, we measure intracardiac pressures with a 22 gauge needle inserted into the aorta close to the aortic cannula and another long 22 gauge needle inserted into the LV through the right ventricular free wall and septum. Left ventricular and aortic pressures are simultaneously monitored and recorded [34]. To measure the provoked pressure gradient, a PVC is elicited and the higher gradient on the postextrasystolic beat (Brockenbrough-Braunwald-Morrow sign) is recorded (Fig. 80.9) [35]. In some patients, small doses of isoproterenol are administered to provoke a gradient. After intracardiac pressures are mea-

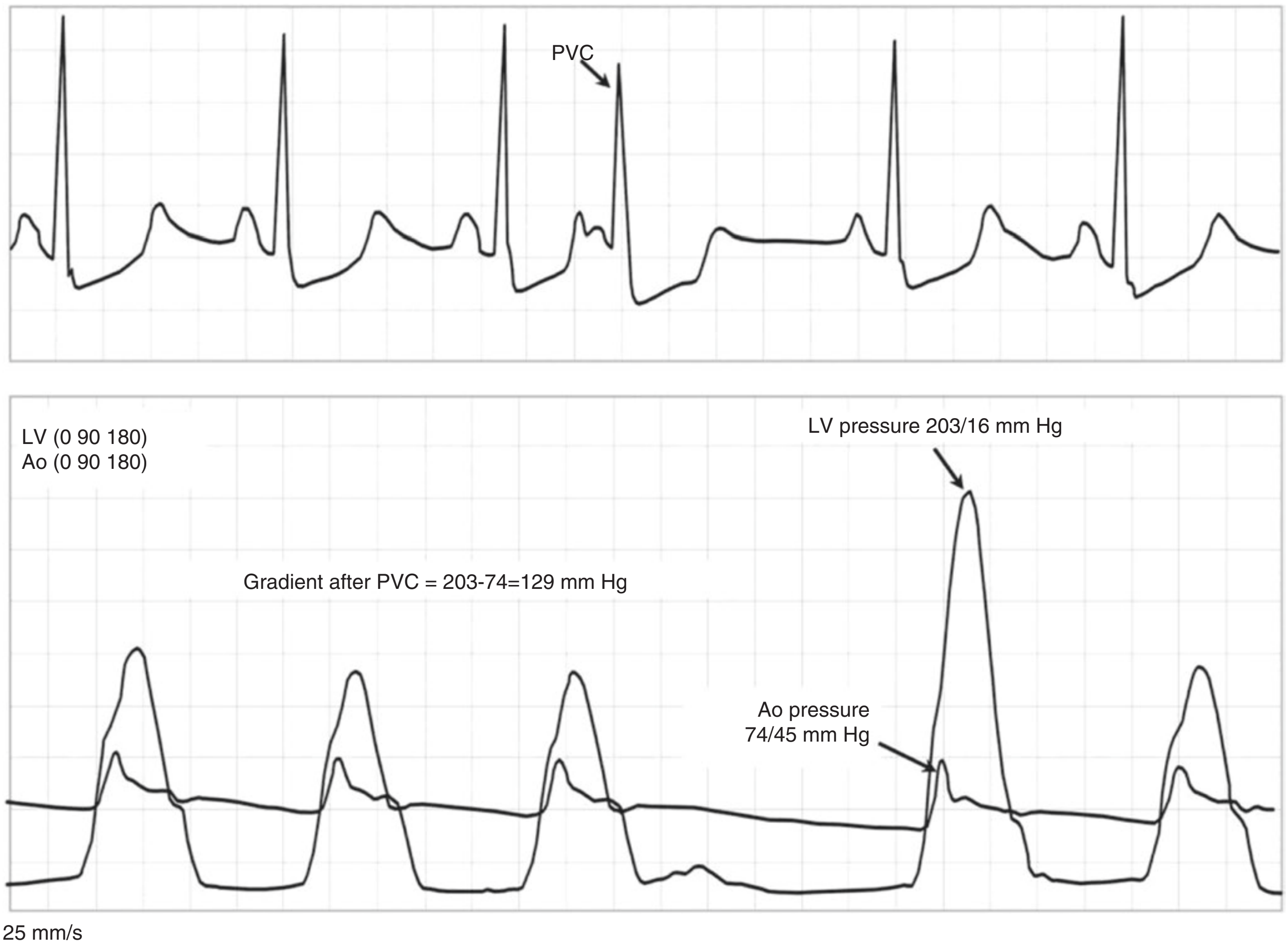


Fig. 80.9 Peak-to-peak left ventricular outflow tract gradient after provocation with premature ventricular contraction (PVC). Pressures in the left ventricle (LV) and in the aorta (Ao) are recorded simultaneously, and peak-to-peak gradient is calculated by subtraction of Ao pressure from LV pressure in systole. Note the gradient increase after PVC. (Reproduced from Ashikhmina et al. [34] with permission of the publisher. Copyright ©2011, Elsevier)

sured, cardiopulmonary bypass is commenced, the aorta is cross-clamped, and cold blood cardioplegia (1000–1200 mL) is infused through the aortic needle vent to arrest the heart.

Adequate exposure of the septum is critically important for myectomy and can be achieved by the following maneuvers. First, the pericardium is elevated toward the surgeon by placing pericardial stay sutures on the right side only. Next, an oblique aortotomy is extended through the midpoint of the noncoronary aortic sinus to a level approximately 1 cm above the valve annulus. Stay sutures are placed in the edge of the proximal aorta, and a cardiotomy sucker is placed through the aortic valve to depress the anterior leaflet of the MV and protect it from injury. The right aortic valve cusp is collapsed against the sinus wall where it will usually stay. A sponge stick is used during myectomy to depress the right ventricle and rotate the septum posteriorly, orienting the LV outflow anteriorly.

A standard No. 10 scalpel blade is used for myectomy. As illustrated in Fig. 80.10, incision in the septum is started just to the right of the nadir of the right aortic sinus and carried upward and then leftward over to the anterior leaflet of the MV. Scissors are used to complete excision of this initial portion of the myocardium. The excision is then deepened and lengthened toward the apex of the LV to extend the area of septal excision beyond the endocardial scar. Trabeculations are excised, and any remaining potentially obstructing muscle is removed using a pituitary rongeur. Adequate septal myectomy usually yields 3–12 g of muscle. Use of the sponge stick to depress and rotate the heart posteriorly will improve exposure of the distal extent of the septal obstruction to be excised (Fig. 80.10 inset). The aortotomy is closed, and the operation proceeds as usual.

This extended myectomy technique differs from the standard Morrow operation in which parallel incisions create a groove in the septum that extends up to 3 cm from the aortic valve [36]. Our procedure which results in a wider excision of muscle in the immediate subaortic area improves exposure of the distal extent of the hypertrophied septum, and

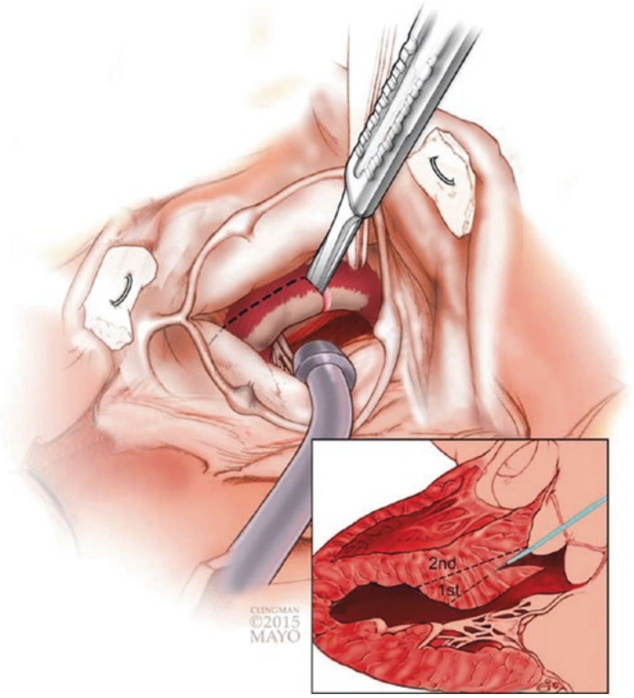


Fig. 80.10 Septal myectomy performed through a low oblique aortotomy extending into the noncoronary sinus. With a no. 10 blade on a long handle, an incision is made in the septum beginning just to the right of the nadir of the right aortic sinus. This incision is carried upward initially and then leftward toward the anterior leaflet of the mitral valve (broken line). In the inset, the initial excision is carried further toward the apex of the left ventricule to remove hypertrophied septum beyond the endocardial scar. (Copyright ©2018, Mayo Foundation)

myectomy extends up to 7 cm from the aortic valve. The technique described above also differs from the method reported by Messmer in which a triple hook retractor is used to pull the septum into view [37]. We believe this is rarely necessary and may predispose to iatrogenic septal defect. Indeed, inadequate myectomy results more often from failure to excise sufficient length of the septum (toward the apex) than from inadequate depth of excision [38]. Importantly, the method we describe has proved adequate for all patients with subaortic obstruction, and we believe that maneuvers such as anterior leaflet plication are unnecessary and potentially harmful.

In most patients with obstructive HCM, SAM-related mitral regurgitation can be relieved or substantially improved by isolated septal myectomy alone. MV repair or replacement is reserved for patients with intrinsic leaflet abnormalities [9, 20]. To confirm complete relief of the LVOT obstruction, direct measurement of the LVOT pressure gradient is repeated after cardiopulmonary bypass when hemodynamics are stable. Intraoperative TEE after septal myectomy can identify residual MR, SAM, and any septal defects created by excision of septal muscle. In general, postmyectomy pressure gradient should be less than 10 mmHg. If the gradient is higher and there is residual SAM, we examine the TEE carefully to identify the site of septal contact. Unacceptable residual gradients are corrected by resumption of cardiopulmonary bypass and repeat transaortic myectomy. If transaortic exposure is poor, the region of septal obstruction causing residual gradient can be approached through an apical incision (Fig. 80.11) [14].

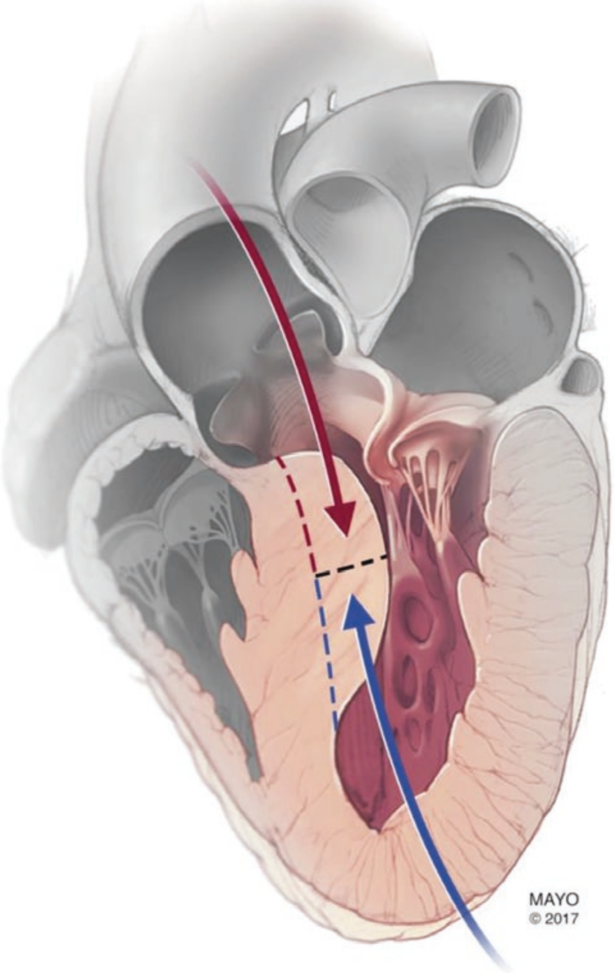


Fig. 80.11 Complex long-segment septal hypertrophy may require both a transaortic approach and a transapical approach. (Copyright ©2018, Mayo Foundation)

For patients with apical hypertrophy or midventricular obstruction that cannot be safely relieved via transaortic myectomy, a transapical approach is indicated. A moist laparotomy pad is placed in the pericardial well behind the LV and the apex of the heart is delivered anteriorly. The left anterior descending coronary artery is identified and a 6–7 cm apical ventriculotomy is made parallel and lateral to it. The incision is located over the apical dimple (when one is present), and it should be positioned approximately 2 cm lateral to the left anterior descending coronary artery to allow secure closure of the ventricle without compromising the vessel.

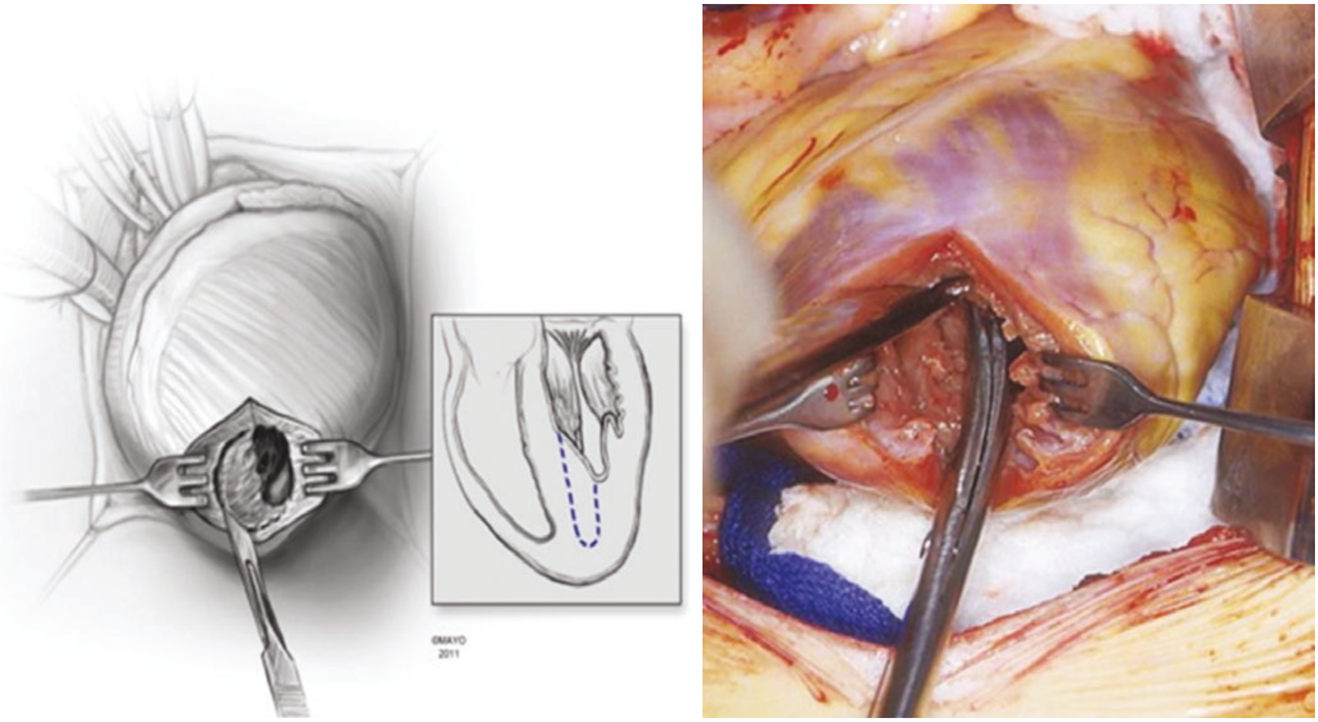


Fig. 80.12 Myectomy is performed removing septal muscle using a No. 10-blade knife and scissors with the aid of small Volkmann retractors. The main focus of the procedure is on the ventricular septum with limited shaving done on the LV free wall (dashed line in the inset). It is important to avoid excessive myectomy adjacent to the ventriculotomy. *LV* left ventricle. (Reproduced from Said et al. [39] with permission of the publisher. Copyright ©2013, Elsevier)

For patients with midventricular obstruction, there is usually an adequate apical space for entrance into the ventricular cavity. The papillary muscles and chordae can be retracted away from the septum with a cardiotomy sucker to facilitate exposure of the hypertrophied septum. Myectomy begins along the septum with removal of the myocardial scar and underlying muscle. Typically there is a septal contact lesion created by the hypertrophied septum and the anterolateral papillary muscle; papillary muscles can be shaved if they are greatly hypertrophied.

In apical HCM, the hypertrophied muscle occupies most of the apical cavity and papillary muscles are displaced apically. The ventricle should be opened cautiously to avoid injury on the papillary muscles and MV apparatus. After the anterolateral and posteromedial papillary muscles are identified and protected, the septal myectomy begins with the main goal of enlarging the volume of the left ventricular cavity (Fig. 80.12) [39]. In many patients it is possible also to remove muscle from the free wall; hypertrophied papillary muscles can be shaved to further increase LV volume. The adequacy and proximal extent of the resection are evaluated by direct inspection and digital palpation. The left ventricular cavity is irrigated to remove muscle debris, and the MV apparatus is explored to ensure that it is not injured. Excessive shaving of the left ventricular wall near the ventriculotomy edges should be avoided as this may cause difficulty in ventriculotomy closure. Two-layer closure of the apical ventriculotomy using strips of Teflon felt is the preferred technique of closure.

The ability to perform concomitant procedures is a significant advantage of myectomy versus non-surgical treatment of obstructive HCM. Coronary artery bypass grafting is indicated for patients with severe lumen stenosis due to atherosclerosis. Myocardial bridging of the left anterior descending coronary artery is not uncommon in patients with HCM and may contribute to symptoms of exertional chest pain and pressure. Coronary artery bridging is considered to be a benign condition [40], but for patients with angina symptoms we unroof the involved coronary artery segment. Atrial ablation with additional appendage ligation is recommended for patients with chronic AF, as this arrhythmia is associated with reduced long-term survival of patients with HCM [30, 41].

Postoperative Management

In contrast to postbypass management of most other cardiac surgical patients, it is important to maintain adequate afterload for HCM patients early following myectomy.

Vasodilators are generally contraindicated, while judicious use of vasopressin or norepinephrine infusions is helpful to maintain adequate peripheral vascular resistance. Atrioventricular synchrony is important for sufficient filling of the hypertrophic ventricle during diastole. AF with rapid response may be poorly tolerated, and prophylactic use of amiodarone and/or beta blocking agents helps to maintain sinus rhythm. Atrial pacing is useful to augment cardiac output in patients with bradycardia and may reduce risk of AF. If supraventricular tachycardia leads to hypotension, early direct current cardioversion should be performed. Other postoperative management pathways and protocols including pain relief, fast-track protocol, early ambulation, and discharge strategy are similar to those used for patients having other cardiac procedures.

Medical treatment with beta blocker is resumed postoperatively with the aim to decrease the preoperative dose by half at hospital dismissal. Calcium channel blockers or disopyramide are not routinely restarted after operation. Before hospital dismissal, TTE is routinely obtained to assess relief of LVOT obstruction, function of cardiac valves, and to exclude presence of pericardial effusion.

Perioperative Results

As seen in Fig. 80.13 and Table 80.1, perioperative mortality following isolated septal myectomy for obstructive HCM is <1% in experienced centers [42]. Major complications are iatrogenic ventricular septal perforation, aortic or mitral valve injury, and complete heart block. The incidences of these complications are low. In our contemporary practice, ventricular septal defects have occurred in <0.5% of patients and permanent pacing for complete heart block is necessary in 2%. For patients who are in sinus rhythm preoperatively with no conduction abnormalities, risk of heart block requiring permanent pacing is 0.6%. Left bundle branch block is a common conduction abnormality following septal myectomy, but does not cause adverse sequelae.

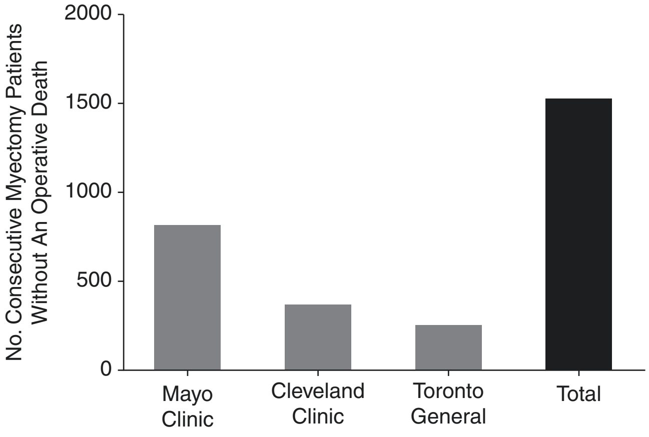


Fig. 80.13 Contemporary low operative risk for septal myectomy. Consecutive number of isolated septal myectomies (without associated cardiac operations or prior alcohol ablation) successfully performed since the last operative death at the three most active North American surgical centers: Mayo Clinic; Cleveland Clinic; and Toronto General Hospital. (Reproduced from Maron et al. [43] with permission of the publisher. Copyright ©2007, Wolters Kluwer Health, Inc.)

Table 80.1 Operative mortality associated with septal myectomy[a] at North American Hypertrophic Cardiomyopathy Centers, 2000–2014

Institution	No. of myectomies	Age (years)	Male (%)	Operative deaths[b]	
				n	%
Mayo Clinic, Rochester, Minnesota	1411	51 ± 14	55	4[c]	0.3
Cleveland Clinic, Cleveland, Ohio	1470[d]	55 ± 14	55	6	0.4
Tufts Medical Center, Boston, Massachusetts[e]	348	52 ± 15	56	4	1.1
Toronto General, Ontario, Canada	306	49 ± 13	62	2	0.6
Mount Sinai–St. Luke's and Roosevelt, New York, New York	160	53 ± 14	48	1	0.6
Totals	3695	54 ± 14	55	17	0.4

[a] Does not include myectomy associated with valve replacement, coronary artery bypass grafting, or resection of a subaortic membrane

[b] Within 30 days of the myectomy

[c] Includes two patients with prior alcohol septal ablation; with these two patients considered nonpure myectomies, the Mayo mortality rate would be only 0.15%

[d] Includes 19% of patients with mitral valve repair

[e] Newest myectomy center with operations performed over only 11 years with first procedure in 2004, whereas data for the other centers encompass 15 years

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Long-Term Outcomes

In patients with obstructive HCM, residual pressure gradients following adequate myectomy are usually eliminated, and recurrent LVOT obstruction is rare. Functional capacity is improved, and symptoms are eliminated or substantially relieved in 80–90% of patients. Long-term survival following septal myectomy is similar to an age and gender matched general population [7] (Fig. 80.14). Importantly, postmyectomy survival is superior to survival of patients with obstructive HCM who are managed medically (Fig. 80.15). As seen in Fig. 80.16, the good late survival following septal myec-

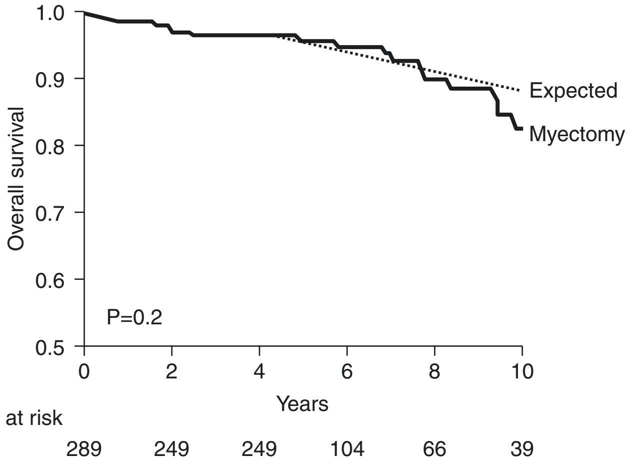

Fig. 80.14 Survival free from all-cause mortality after septal myectomy for obstructive hypertrophic cardiomyopathy (n = 289) compared with the age- and gender-matched general U.S. white population. Log-rank, p = 0.2. (Reproduced from Ommen et al. [7] with permission of the publisher. Copyright ©2005, Elsevier)

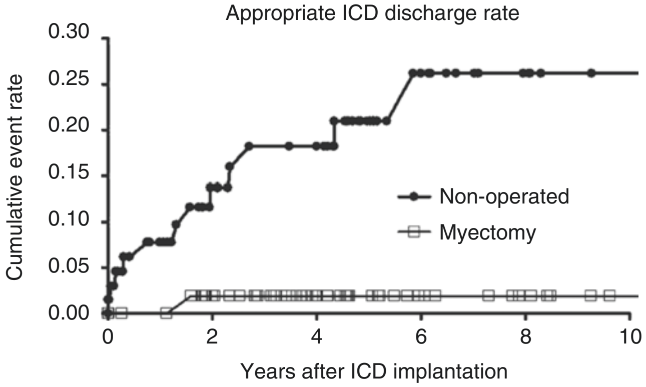

Fig. 80.16 Implantable cardioverter defibrillator discharge rates in patients following septal myectomy (n = 56) compared to unoperated patients with hypertrophic cardiomyopathy (n = 69). Average annualized implantable cardioverter defibrillator discharge rates of 0.24% in the myectomy group, compared with 4.3% in the non-myectomy group (P = 0.004). (Reproduced from McLeod et al. [8] with permission of the publisher. Copyright ©2007, Oxford University Press)

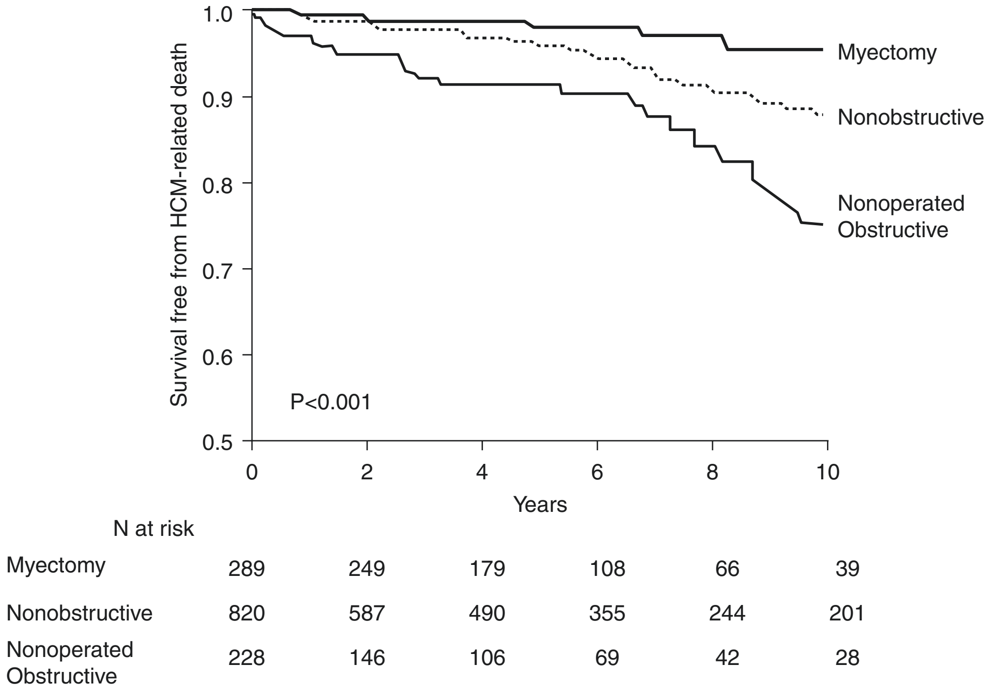

Fig. 80.15 Survival free from hypertrophic cardiomyopathy-related death among patients in three subgroups: surgical myectomy (n = 289), nonoperated with obstruction (n = 228), and nonobstructive (n = 820). Overall log-rank, p < 0.001; myectomy versus nonoperated obstructive hypertrophic cardiomyopathy, p < 0.001; myectomy versus nonobstructive hypertrophic cardiomyopathy, p = 0.01. (Reproduced from Ommen et al. [7] with permission of the publisher. Copyright ©2005, Elsevier)

tomy may be due to reduced risk of ventricular arrhythmias. In a study of patients who had ICDs implanted, McLeod and associates documented that at a median follow-up of 4 years, appropriate discharges occurred in only one (2%) patient who had previous myectomy compared to 12 (17%) patients in the non-myectomy group (annualized event rate 0.24% versus 4.3% per year, $p < 0.004$) [8].

Patients undergoing apical myectomy also experience significant improvement of symptoms [17]. Apical myectomy provides an alternative to heart transplantation for patients with severe diastolic heart failure due to apical HCM.

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Left Ventricular Volume Reduction

81

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High Yield Facts

- Ventricular remodeling after an acute myocardial infarction (AMI) includes changes in shape and, more importantly, in volume, together with a reduction of the systolic function, measured as ejection fraction or other parameters.
- Left ventricular volume reduction (LVVR) was conceived to reverse symptoms of heart failure by reducing LV size, improving, as a consequence, the systolic function.
- From late 1980s, the Dor procedure, with some modifications, has remained the most utilized procedure for LVVR.
- Guilmet published another technique, the 'overcoat technique', which combines the reduction in volume with a more conical shape.
- A sphericity index as low as possible must be one of the goals of LVVR.
- The prevalence of patients with mitral regurgitation who need mitral valve surgery while having LVVR is increasing.
- Survival at 5 years and 20 years has been reported as 60% and 36.1%, respectively.
- Freedom from cardiac death is higher in patients who underwent shape-related LVVR (86.6% vs. 76.3%, P = 0.032).

Introduction

Ventricular remodeling after an acute myocardial infarction (AMI) includes changes in shape and, more importantly, in volume, together with a reduction of the systolic function, measured as ejection fraction (EF) or other parameters. The left ventricular (LV) dilatation and thinning, which follow AMI, increase wall stress and, due to the inability of the remaining myocardium to compensate, cause further LV remodeling. Moreover, extensive ventricular dilatation limits the benefits of isolated myocardial revascularization [1, 2], as patients with larger ventricular sizes show no improvement in the systolic function and have higher incidence of cardiac death, MI and hospitalization for heart failure.

Rationale for Left Ventricular Volume Reduction

The effects of the AMI on ventricular shape are related to Laplace's law ($\sigma = Pr/2h$), which states that, at a constant ventricular pressure (P), an increased radius (r) of curvature (consequent to a full thickness infarction) and a decreased wall thickness (h) (consequent to the thinning of the infarcted wall) contribute to increasing tension (σ) of the myocardial muscle fibers and promote further deformation and expansion of the infarcted ventricular wall.

Left ventricular volume reduction (LVVR) was conceived to reverse symptoms of heart failure by reducing LV size, improving, as a consequence, the systolic function in patients with remodeled heart after an MI, mainly in the left anterior descending (LAD) territory.

Surgery for exclusion, or resection, of aneurysmal portion of the LV became routine after Cooley et al. [3] described, in 1958, a linear resection of the anteroapical wall, which remained for many years the golden standard.

In the late 1980s, Dor reported a volume-related technique that remained, with some modifications (addition of

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the Fontan stitch and introduction of a shaper) [4], the most utilized procedure for LVVR [5]. The aim of the Dor technique is reduction in the LV volume, irrespective of the shape obtained. In the same decade, Guilmet et al. [6] published another technique, which combined the reduction in volume with a more conical shape, the 'overcoat technique', a re-interpretation of operation proposed by Stoney et al. [7]. This procedure remained obsolete for many years until our group, in search of more physiological solutions for surgical LV remodeling, rediscovered this elegant solution in 1998 and, with some substantial modifications aimed to make the technique more surgically appealing. We started its clinical application under the name of linear septoexclusion (Fig. 81.1) [8] that, not only aims to achieve volume reduction but also rebuilds the shape as conical as possible thereby becoming a part of the shape-related techniques. The linear suture (anterior wall to septum) is mainly used in large hearts. When the volumes are intermediate, the linear suture is replaced by an oval patch of different sizes (to obtain a reasonable end-diastolic volume), tailored in such a way that the new apex is as distal as possible, to maintain a sphericity index as low as possible. This evolution is called septal reshaping [9] (Fig. 81.2).

Volume-Related or Shape-Related Left Ventricular Reduction

The normal LV shape is the half of a prolate ellipsoid with its long axis directed from apex to base, and its inflow and outflow being in continuity. LV ejection and filling is a function of systolic twisting and diastolic untwisting, which depends on the angular orientation of the oblique muscular fibers that are unique to the LV [10]. A minor change of 5–10° in the fiber orientation, as happens in more spherical heart, affects ventricular torsion and myocardial performance [11]. A change in sphericity seriously affects the LV function. A myofibril contraction of 15% in a ventricle with a normal sphericity index (0.5, ellipsoid shape) generates an EF of 62%. Conversely, with 15% fibers contraction, the EF falls below 40% if the sphericity index approaches 1 (spherical shape) and goes up to ≥80% if the sphericity index approaches 0 (extreme ellipsoid) [12]. Thus, a sphericity index as low as possible must be one of the goals of LVVR. These concepts are the basis of the techniques aimed to reduce the LV volume while maintaining a conical shape, the shape-related techniques. However, the most utilized technique, the Dor procedure, is volume-related, with the main goal being volume reduction, independently from the

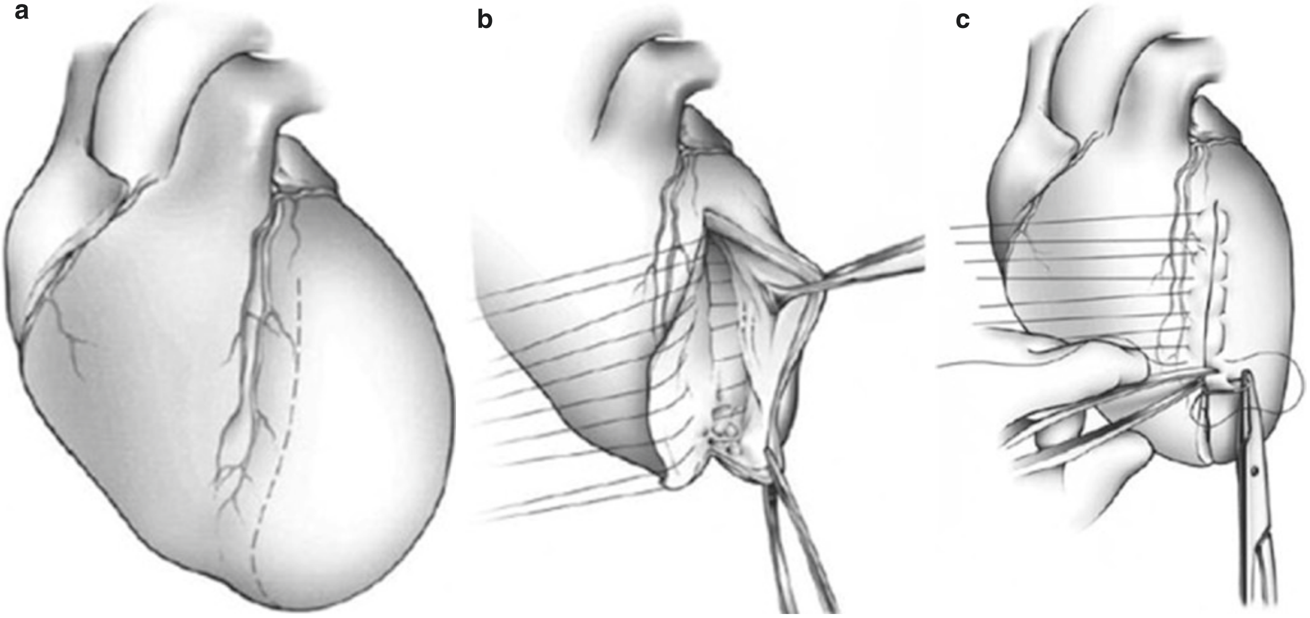

Fig. 81.1 Linear septoexclusion. After the scar is incised parallel to left anterior descending (LAD) artery (**a**), the free wall is sutured with U stitches deep in the septum, at the border between scarred and healthy muscle in both sides (**b**). The ventriculotomy is then closed (**c**). (From Calafiore et al. [8] with permission)

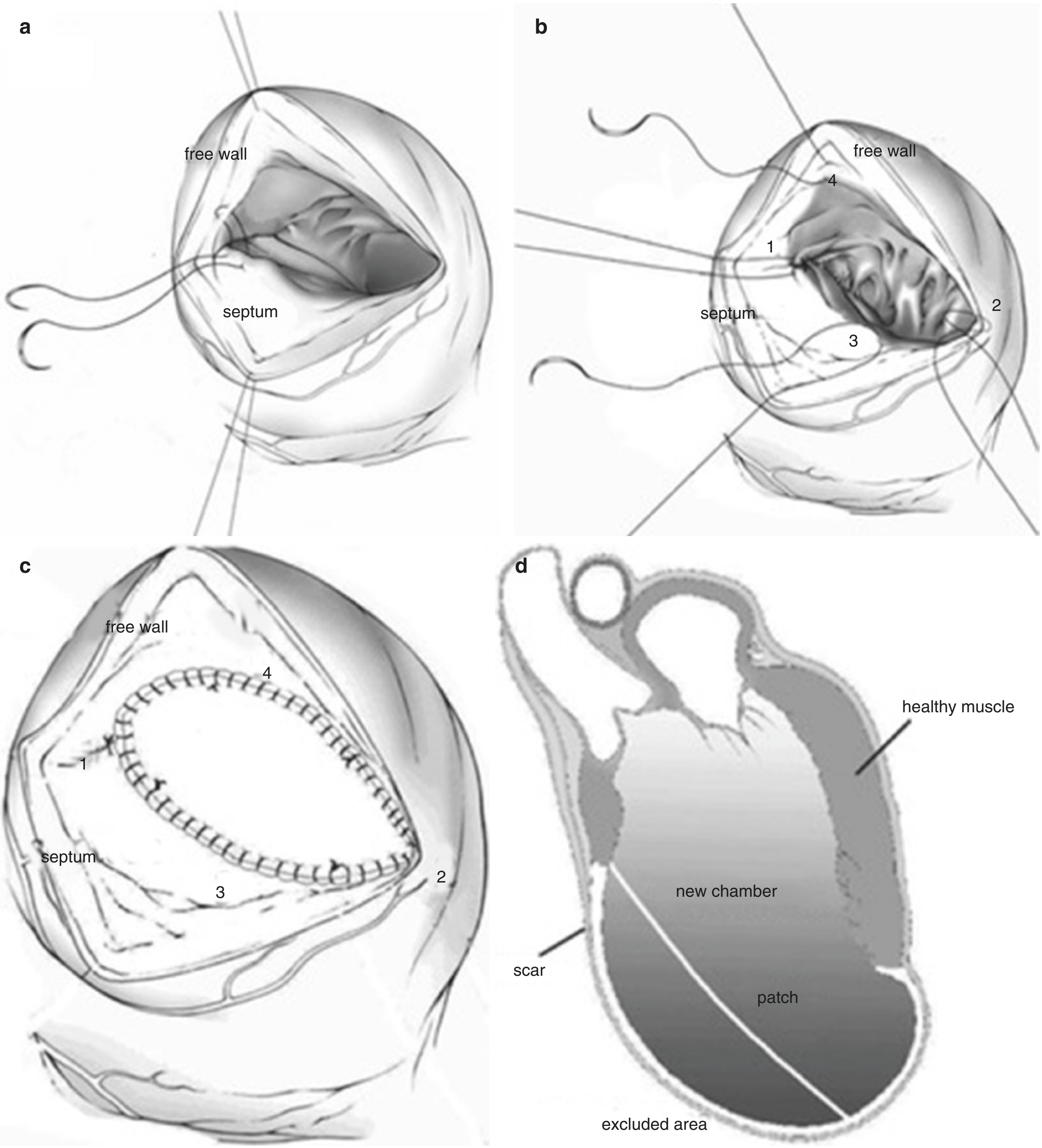
a
free wall
septum
b
free wall
4
1
septum
2
3
c
free wall
4
1
septum
3
2
d
healthy muscle
new chamber
scar
patch
excluded area

Fig. 81.2 Septal reshaping. (**a**) The anterior wall is joined to the septum by means of an oblique linear suture with one or two polyester (Ti-cron 2-0) U-stitches. (**b**) Four stitches are passed: at the end of the last interrupted suture (1); at the level of the new apex (2); deep in the septum at the border between the scar and the healthy posterior septum (3); and in the anterior wall, again at the limit of the scar (4). (**c**) An oval polyethylene terephthalate fiber (Dacron) patch is tailored and fixed with the four stitches previously placed. (**d**) Purpose of the procedure is to create a new ventricular chamber that has a more conical shape and excludes the anteroseptal scar. (From Calafiore et al. [33], with permission)

shape, as the sphericity index often increases, irrespective of the use of a ventricular shaper [13, 14]. The regional shape shows no significant changes, as indices of curvature often remain unchanged. Choi et al. [15] showed that a low curvature wall was characterized by a maximum in the transmural fibers stress and strain in the mid-wall region, while a steep subendocardial transmural gradient was present in a high curvature wall. As a consequence, in a clinical setting, end-diastolic elastance increases after surgery, showing a worsening diastolic function [16]. The diastolic dysfunction causes the Starling relationship to be depressed in most of the patients. Of 12 patients studied by Lee et al. [14], the predicted Starling relationship remained unchanged in three, worsened in eight and improved only in one. Other studies reported similar findings [17]. This is reflective of reduced stroke volume at rest [13, 18] and failure to increase adequately the cardiac output under effort. In general, the improvement in systolic function is counterbalanced, in most cases, by worsened diastolic function. Other important information was provided by a fluid dynamic model of the normal LV and of an LV after the Dor procedure, described by Doenst et al. [19]. They found that, in the normal heart, the fluid dynamic was such that only 2% of the blood that entered the LV during diastole remained in the cavity after four cycles. After surgery, LV geometry became apple-shaped and the fluid dynamics were completely changed. Blood stagnated into the apex and was no longer redirected towards the outflow tract. As a consequence, 39% of the blood entering LV in diastole was still present in the cavity after four cardiac cycles. Blood washout was in any case similar before and after surgery.

This analysis reflects the core problem of ventricular reduction surgery: the benefits anticipated with surgical reduction in LV volume are counterbalanced by a reduction in diastolic distensibility [20]. The Dor procedure causes an increase in the EF, which is not a valid surrogate of the improvement in the systolic function, as LVVR, reducing by definition the end-diastolic volume, causes an increase in EF to different extents, independently of the effective stroke volume. Reduction in mechanical dyssynchrony [17, 18] improves mechanical efficiency and global LV performance through an improved synergic distribution of regional stress during the isovolumic contraction and relaxation phases. Globally, we can agree that the Dor procedure improves systolic function and mechanical efficiency by reducing LV wall stress and mechanical dyssynchrony, and increasing EF. However, concomitant revascularization of dysfunctional myocardium contributes to improved systolic performance as well and therefore the impact of the single procedure on global improvement is then impossible to quantify. Even with some limitation, the Dor procedure, a volume-related technique, provides good results in presence of large volumes due to diskinetic areas.

In the recent era the need for a more physiological shape is associated with the changing pattern of septoapical scars. In the past, when dyskinetic areas were the most common consequence of acute anterior myocardial infarction, dilation was predominant, and volume reduction was relatively easy to perform. More recently, myocardial infarction is often not completely transmural. As the left anterior descending (LAD) artery remains open (due to spontaneous fibrinolysis or primary angioplasty), part of the anterior wall and of the septum are replaced by akinetic muscle, consisting of a mixture of scar and epicardial muscle salvaged by reperfusion. This anatomical aspect prevents the involved region from collapsing after cardiac decompression in the operating theatre. However, these patients present with worse hemodynamic parameters and lower LV compliance. The reduction of distensibility increases the end-diastolic pressure (and consequently pulmonary pressure) and affects remote zones earlier than in patients with dyskinetic areas. The remote zone is often hypocontractile, remodeled and represents, in extreme cases, an undefined zone between scarred and healthy muscle. Furthermore, regional infarction can initiate a myopathic process which can spread beyond the immediate peri-infarct region and may involve the entire ventricle. This process offers an explanation for the progressive dysfunction and ventricular dilation that occur in some patients after a single myocardial infarction. When, progressively, dilation of the uninvolved zone becomes predominant and dilated cardiomyopathy occurs, medical treatment and surgical options become ineffective and temporary, with the exception of heart transplant [21].

In addition, volumes in the earlier phase are not as large as previously. Furthermore, the extent of the dilation is not uniform. The involvement of the septum and of the anterior free wall often differs, due to the anatomy of the branches of the LAD. Diagonal branches often originate at an angle of 45°; the involvement of the anterior free wall then forms a triangle, with the apex in the upper portion. Septal branches originate at an angle of 70–90°; involvement of the septum then starts as high as the anterior free wall but goes deeper. The septum bulges towards the right ventricle, minimizing the external dilation. This phenomenon is central to techniques which are aimed more at LV volume reduction while maintaining a conical shape than at isolated volume reduction.

Secondary Mitral Regurgitation

The prevalence of patients with mitral regurgitation who need mitral valve (MV) surgery while having LVVR is increasing. In a study of ours, the prevalence of MV surgery was 84.1% [22] versus 28% in the experience of Castelvecchio et al. [23], 18% in the Surgical Treatment for Ischemic Heart Failure

(STICH) trial [24] and 18.6% in the report from Dor et al. [25]. The increase in prevalance of mitral regurgitation needing correction is a mirror of the high prevalence of akinetic compared with dyskinetic areas, causing higher grade of LVEDD and more complex remodeling of the mitral valve.

The STICH Trial

In 2009 a randomized controlled trial, the STICH (Hypothesis 2) trial, was published [24]. In this study, 1000 patients were allocated to receive coronary artery bypass grafting (CABG) alone (n = 499) or CABG and LVVR (n = 501). The results clearly showed that there was no benefit in adding LVVR to patients who had CABG, both in terms of survival and clinical improvement. This paper was criticized [26] for many reasons. To summarize, initially patients had to be selected according to "absent viability in the anterior ventricle by nuclear scan determination, LV end-systolic volume index (LVESVI) ≥60 ml/m^2, and akinesia ≥35% of the anterior wall". Centers were selected according to their capability to use cardiac magnetic resonance (CMR) to evaluate both volumes, scars and EF. Echocardiography was specifically excluded for measuring LV volume because of its inaccuracy when regional asynergy is present. However, STICH enrolled a quite different group of patients, namely those with NYHA Class II–IV congestive heart failure (within 3 months of entry), coronary artery disease that was amenable to CABG, an EF ≤ 35% [defined by echocardiogram, left ventriculogram, CMR, or gated single photon (SPECT) studies], and 'dominant anterior left ventricular dysfunction'. Accurate viability and LV volume were not done in all patients as planned.

Goal of LVVR was to obtain, after 4 months from surgery, an increase in EF of ≥10% and a decrease of ≥30% in LVESVI. Measurement were performed only in 38% of the patients and the average LVESVI was 19%. Although the debate was intense, the STICH (Hypothesis 2) trial proved to be the tombstone of LVVR, which slowly became an obsolete procedure.

During the subsequent years some sub studies were published, showing that some of the criticisms of the STICH (Hypothesis 2) trial were correct. In one such study, myocardial viability was measured with four validated SPECT protocols in 267 patients [27]. Out of them, 191 (72%) showed viability in the anterior wall or apex. These patients needed to be better evaluated before any surgical decision, as most of the patients needed only revascularization.

Michler et al. [28] evaluated 555 patients who had paired echocardiograms (before and 4 months after surgery), 296 treated with CABG only and 259 with CABG and LVVR. The number of deaths was similar (67/296, 22.6%, in CABG only and 49/259, 18.9%, in CABG and LVVR, p = 0.283). In the subgroup of patients who had CABG and LVVR, postoperative LVESVI was <60 ml/m^2 in 122 patients and ≥60 ml/m^2 in 137. The number of deaths was very low in the first group (12/122, 9.8% versus 37/137, 27.0%, p < 0.001). The comparison between the deaths in the CABG only patients (67/296, 22.6%) and in the group with CABG and LVVR and postoperative LVESVI <60 ml/m^2 (12/122, 9.8%) showed the higher survival when patients were correctly operated on (p = 0.003). Similar benefit was found comparing the deaths in the CABG only patients and CABG and LVVR patients where the postoperative LVESVI was reduced by ≥30% (67/226, 22.6%, versus 13/96, 13.5%, p = 0.057). Even if the p value was not significant, the difference of 9.1% is clinically significant.

These studies showed that the STICH 2 trial had some intrinsic flaws in its own conduct. At the same time they showed that, when LVVR is performed correctly in the right patients, results are definitely better than CABG only in similar patients.

Clinical Results

The outcome of patients who underwent the Dor operation is satisfying. Survival at 5 years ranges from 61.5% to 72.9% [29, 30]. In a study of ours, 5- and 20-year freedom from death due to any cause has been 60% and 36.1%, respectively [31]. Only a few papers compared volume-related techniques with shape-related techniques. Isomura et al. [32] reported a 7-year survival of 61.5% vs. 72.1%, respectively (P = 0.041), and our group showed improved freedom from cardiac death in patients who underwent shape-related LVVR (86.6% vs. 76.3%, P = 0.032) [29, 33]. In that study, we confirmed that, after 10 years from surgery, clinical results still favor techniques aimed to obtain a more conical shape together with a reduction in volume.

Recently our group reported an experience matured after the publication of the STICH trial, when indications became more restrictive, akinetic areas were predominant (86.7% of the cases), mitral regurgitation needing correction was present in 84.1% of the patients and 1/3 of the cases had severe LVDD. Nevertheless, clinical outcome was satisfying, with 5-year survival of 73 ± 5, reaching 80 ± 5 in elective patients [22].

Conclusions

LVVR is a complex procedure which interferes with some aspects of ventricular contractility that sometimes are not well known. The number of cases subjected to LVVR have reduced, either because of the results of the STICH 2 trial or because the prevalence of primary angioplasty limits the post-infarct dilatation of the LV. Moreover, the exposure of young surgeons to deal with this pathology is scarce with limited experience to perform a safe procedure. However, one must not forget that, when indicated, LVVR is a procedure which can change dramatically the outcome of patients who, in most cases, have no other alternatives.

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Renal Failure After Cardiac Surgery

82

Marc Vives and Juan Bustamante-Munguira

High Yield Facts

- The incidence of cardiac surgery associated acute kidney injury (CSA-AKI) is reported to be up to 30%.
- AKI requiring dialysis (AKI-D) occurs in up to 4% of cardiac surgery cohorts.
- AKI-D results in significantly increased mortality of up to 63%.
- The Kidney Disease Improving Global Outcomes (KDIGO) criteria for AKI staging demonstrate greater sensitivity to detect AKI and to predict associated in-hospital mortality.
- There are several well-recognized independent risk factors for CSA-AKI. Preoperative renal impairment [estimated glomerular filtration rate (eGFR) <60 ml/min, creatinine >2.1 mg/dl] is the most predictive of CSA-AKI.
- Current approaches to prevent CSA-AKI include deferring elective surgery until there is adequate recovery following pre-existing renal injury, careful preoperative risk stratification of patients and consideration of less invasive procedures in those at greatest risk.
- Prompt diagnosis of AKI by panels of biomarkers with early treatment using renal replacement therapy may improve outcomes.

Introduction

Depending on the definition used, the incidence of cardiac surgery associated acute kidney injury (CSA-AKI) is reported to be up to 30% [1]. Data suggest that even a small increase (0.3–0.5 mg/dl) in serum creatinine (sCr) after cardiac surgery is associated with a nearly threefold increase in 30-day mortality, while a larger increase of >0.5 mg/dl is associated with more than an 18-fold increase in 30-day mortality [2]. AKI requiring dialysis (AKI-D) occurs in up to 4% of cardiac surgery cohorts [3–5] and results in significantly longer in-hospital stay and notably increased mortality of up to 63% [6]. In this chapter, we will focus on the pathogenesis, risk prediction, early diagnosis using biomarkers and promising protection strategies for CSA-AKI.

Defining Cardiac Surgery Associated Acute Kidney Injury

The Kidney Disease Improving Global Outcomes (KDIGO) criteria for AKI staging [7] demonstrate greater sensitivity to detect AKI and to predict associated in-hospital mortality (Tables 82.1 and 82.2), than do the risk, injury, failure, loss, end-stage kidney disease (RIFLE) or acute kidney injury network (AKIN) criteria [8]. These criteria, which essentially merge the RIFLE and AKIN criteria, have become the new consensus definition of AKI and can be used to diagnose CSA-AKI. However, the main limitation of these definitions is that they rely on sCr, which is known to be a less-than-ideal biomarker for AKI.

Table 82.1 Acute kidney injury definition

Acute kidney injury is defined as one of the following:
• An increase in serum creatinine by ≥0.3 mg/dl (≥26.5 μmol/l) within 48 h
• An increase in serum creatinine to ≥1.5 times baseline within the previous 7 days
• Urine volume ≤0.5 ml/kg/h for 6 h

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Table 82.2 Proposed KDIGO staging of acute kidney injury

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline or ≥0.3 mg/dl (≥26.5 μmol/l) increase	<0.5 ml/kg/h for 6–12 h
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ≥12 h
3	3 times baseline or ≥4.0 mg/dl (≥353.6 μmol/l) increase or initiation of RRT or in patients <18 years a decrease in eGFR <35 ml/min/1.73 m^2	<0.3 ml/kg/h for ≥24 h or anuria ≥12 h

eGFR estimated glomerular filtration rate, *KDIGO* Kidney Disease Improving Global Outcomes, *RRT* renal replacement therapy

Pathogenesis of Cardiac Surgery Associated Acute Kidney Injury

The pathophysiological features of CSA-AKI are complex and multifactorial including numerous factors: exogenous and endogenous toxins, metabolic factors, ischaemia–reperfusion injury, microembolization, neurohormonal activation, inflammation, oxidative stress and haemodynamic factors (Table 82.3). These mechanisms of injury are likely to be active at different times with different intensities, are interrelated and probably synergistic (Fig. 82.1).

Risk Factors and Prediction of Cardiac Surgery Associated Acute Kidney Injury

There are several well-recognized independent risk factors for CSA-AKI. They include female sex, preoperative cardiac function (cardiogenic shock, New York Heart Association IV, reduced left ventricle ejection fraction (LVEF), presence of congestive heart failure, preoperative use of an intra-aortic balloon pump), diabetes mellitus, peripheral vascular disease, chronic obstructive pulmonary disease, emergent surgery, reintervention, intraoperative use of aprotinin and preoperative renal impairment [estimated glomerular filtration rate (eGFR) <60 ml/min, creatinine >2.1 mg/dl] [3–5, 9, 10]. This last factor is perhaps the most predictive of CSA-AKI. Other risk factors relate to the operative procedure, such as cross-clamp time, duration of cardiopulmonary bypass (CPB), complexity of the surgery [5, 10, 11], transfusion of packed red blood cells (PRBC) and haemodilution on CPB.

The Cleveland Clinic Score [5], the Mehta Score [4], and the Simplified Renal Index (SRI) score [3] are validated for predicting severe AKI that requires dialysis. New predictive models for CSA-AKI, including intraoperative factors, have been recently published from the Cleveland database. Data suggest that these new models improve performance compared with previous predictive scores [12, 13].

Table 82.3 Pathophysiological factors in cardiac surgery associated acute kidney injury

Preoperative	Intraoperative	Postoperative
Prerenal azotemia	Decreased renal perfusion	SIRS
Impaired LV function	Hypotension	Low CO
Recent over-diuresis	Anaesthetic effect	Volume depletion
Nephrotoxins	Autoregulation impairment	Sepsis
Intravenous contrast	DM	
Other drugs	Vascular disease	
Renovascular disease	Nephrotoxics	
	Free iron and free haemoglobin	
	SIRS	
	Embolic events	
	Haemodilution	

CO cardiac output, *DM* diabetes mellitus, *LV* left ventricle, *SIRS* systemic inflammatory response syndrome

Renal Protective Strategies

Preoperative Strategies

Optimization of Renal Function

Delaying elective surgery for renal function optimization in patients with reversible AKI, avoidance of nephrotoxins (such as non-steroidal anti-inflammatory agents, aminoglycoside antibiotics, radiocontrast agents, angiotensin converting enzyme [ACE] inhibitors and angiotensin receptor blockers [ARBs]), optimization of cardiac output for congestive heart failure and correction of intravascular volume depletion should be considered (Table 82.4).

Aspirin

Current data show that preoperative aspirin therapy is associated with a significant decrease in the risk for 30-day mortality and postoperative renal failure [14]. Subgroup of patients with eGFR <60 ml/min may have further benefit from using preoperative aspirin [15].

Statins

Recent trials show no benefit from starting statins preoperatively [16, 17].

However, continuation of statins until the day of surgery should be considered [18].

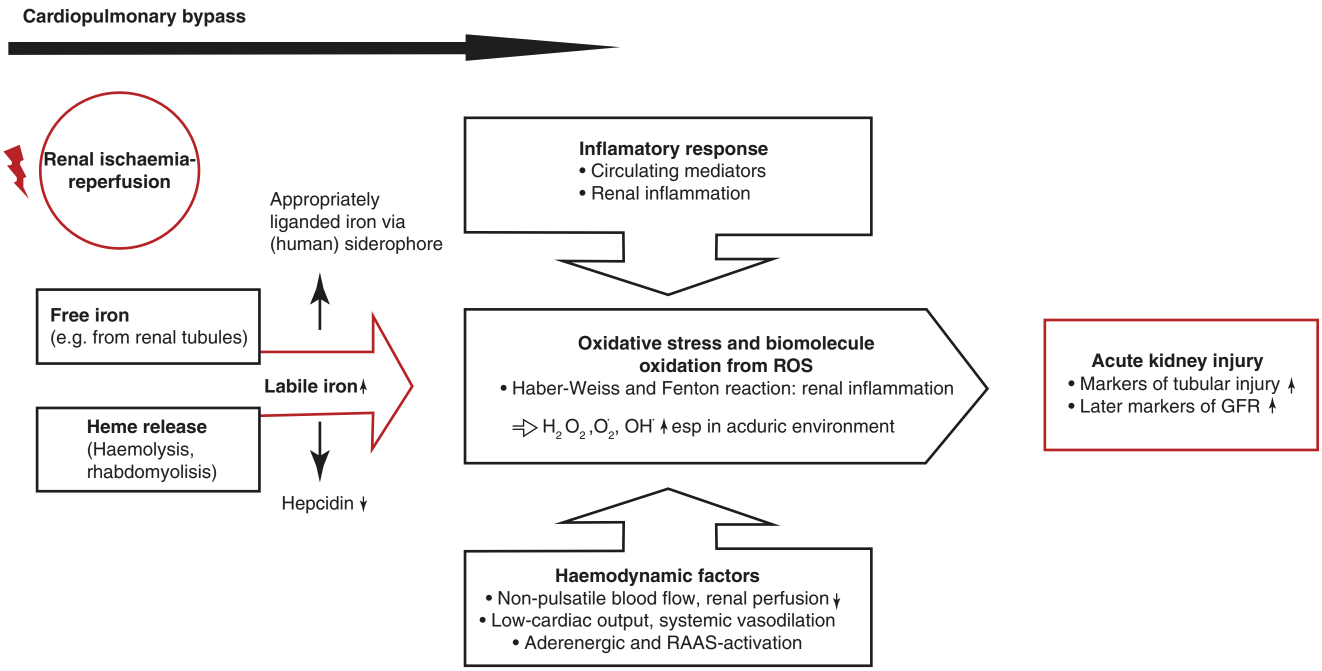
Cardiopulmonary bypass
Renal ischaemia-reperfusion
Appropriately liganded iron via (human) siderophore
Free iron (e.g. from renal tubules)
Labile iron ↑
Heme release (Haemolysis, rhabdomyolisis)
Hepcidin ↓
Inflamatory response
• Circulating mediators
• Renal inflammation
Oxidative stress and biomolecule oxidation from ROS
• Haber-Weiss and Fenton reaction: renal inflammation
⇒ H2O2, O2·, OH· ↑ esp in acduric environment
Haemodynamic factors
• Non-pulsatile blood flow, renal perfusion ↓
• Low-cardiac output, systemic vasodilation
• Aderenergic and RAAS-activation
Acute kidney injury
• Markers of tubular injury ↑
• Later markers of GFR ↑

Fig. 82.1 The role of ischaemia–reperfusion injury during CPB and of reactive oxygen species (ROS), poorly ligated iron and iron metabolism regulators in affecting renal injury. *GFR* glomerular filtration rate, *RAAS* renin–angiotensin–aldosterone system

Table 82.4 Interventions associated with a decreased risk of acute kidney injury after cardiac surgery

Preoperative	Intraoperative	Postoperative
Adequate hydration and avoid loop diuretics	Avoid anaemia	Start statin when feasible
Surgery after 5 days of coronary angiography	Avoid haemodilution	Avoid nephrotoxic agents
Statin use	Off-pump CABG	Use of early (<3 days) RRT
Anaemia optimization	Use of intra-aortic filtration	
	Use of atrial natriuretic peptide	
	Use of fenoldopam	
	Shorter duration of CPB	
	Optimal glucose control	

CABG coronary artery bypass grafting, *CPB* cardiopulmonary bypass, *RRT* renal replacement therapy

Erythropoietin

It is reasonable to use preoperative erythropoietin (EPO) plus iron (especially if ferritin is <100 mg/L), given several days before surgery, in patients with preoperative anemia (Hb <12.5 g/dL), candidates for operation who refuse transfusion (e.g., Jehovah's Witness) and in patients who are at high risk for postoperative anemia. However, chronic use of EPO is associated with thrombotic cardiovascular events in renal failure patients suggesting caution for this therapy in individuals at risk for such events (e.g., coronary revascularization patients with unstable angina).

Intraoperative Strategies

Anemia Correction

There is evidence to suggest that low preoperative and intraoperative haemoglobin levels are associated independently with CSA-AKI [19], but unfortunately, there is also evidence to suggest that intraoperative transfusion is independently associated with CSA-AKI [10, 19]. 2011 STS/SCA blood conservation guidelines suggest that transfusion to keep the Hb >7 g/dL during CPB, for patients at risk for end-organ ischemia/injury, may be considered (grade 2b) [20].

TRICS-III trial showed no difference in primary outcome (a composite outcome of death from any cause, myocardial infarction, stroke, or new-onset renal failure with dialysis) comparing hemoglobin 7.5 g/dL vs. 9.5 g/dL as a trigger for transfusion of RBC intraoperatively and postoperatively in the ICU [21].

Blood Glucose Control

Hyperglycemia (>180 mg/dL) should be avoided during the perioperative period, with caution to avoid also hypoglycemia.

Blood Management Program

The initiation of a program on blood management decreases the rate of RBC, platelets and fresh frozen plasma transfusion, as well as the rate of AKI (34% relative risk reduction; p 0.039) and the associated healthcare cost. This program consists of transfusion thromboelastography-guided, preoperative anemia optimization, restrictive threshold for intraoperative transfusion, retrograde autologous priming, reduced volume of the bypass circuit and increase use of cell saver and tranexamic acid [22].

Mini-CPB and Zero-Balanced Ultrafiltration

Based on current data, use of mini-CBP [23, 24] and zero-balanced ultrafiltration during CPB, especially for patients with eGFR <60, may be also considered [25].

A goal-directed perfusion initiative aiming for delivery of O_2 (DO_2) >300 ml with mean arterial pressure (MAP) >70 mmHg during CPB plus zero-balanced ultrafiltration, was associated with a significant reduction of AKI at 72 h (23.9% vs. 9.1%) [26]. Hence, based on current data, MAP >70 mmHg and DO_2 >300 ml O_2/min/m during CPB should be considered.

Surgical Strategies

The CORONARY trial suggest that Off-pump Coronary Artery Bypass (OPCAB) grafting was associated with no significant differences in renal replacement therapy (RRT) requirement [HR 1.04 (95% CI 0.61–1.76), P = 0.59]. However, a definition for initiation of RRT was lacking. Hence, patients with the same clinical situation might have been managed differently. Furthermore, OPCAB was associated with a significant decrease in mild AKI, defined by RIFLE-risk [HR, 0.87 (0.76–0.98), P = 0.02] or AKIN stage 1 [HR, 0.87 (0.80–0.96), P = 0.01]. The CORONARY trial at 1 year and 5-years follow-up showed no difference in RRT requirements. However, mild AKI was not analysed [27, 28].

Volatile Anesthesia

A meta-analysis of 1600 patients, from ten randomised controlled trials (RCTs), showed that volatile anesthesia is associated with a decrease risk of AKI (RR 0.65; 0.43–0.97, p = 0.04), compared to total intravenous anesthesia. Volatiles have a known effect of Ischemic/reperfusion injury attenuation. Hence, based on current data, use of volatile anesthetics, should be considered [29].

Remote Ischemic Preconditioning

The Renal RIP trial showed a significant reduction in the incidence of major adverse kidney events (death, RRT and persistent renal dysfunction) at 90 days (14.2% vs. 25%, p = 0.034), associated with the use of remote ischemic preconditioning (rIPC) in high risk patients with Cleveland Score ≥6. Moreover, AKI patients in rIPC group recover faster. They observed that the effect of rIPC is attenuated by propofol. Hence, based on current data, use of remote Ischemic pre-conditioning in high risk patients with Cleveland Score ≥6, without using propofol, may be considered [30, 31].

Balanced Crystalloid Solutions

The LICRA trial with 1136 patients showed no differences in AKI—KDIGO II and III—at 5 days, comparing 0.9% Saline with buffered salt solution [32]. However, in our opinion, given the existing data showing increase risk of AKI with 0.9% saline in ICU patients, balanced crystalloid solutions should be used, unless hyponatremia is present.

Fenoldopam

It has been suggested that the use of prophylactic fenoldopam, a selective dopamine receptor-1 agonist, during cardiac surgery, might have a renoprotective effect. Unfortunately, a definitive recent multicenter RCT on 667 patients was stopped for futility in the interim analysis [33].

Natriuretic Peptide

Natriuretic peptide may induce natriuresis and vasodilatation by opposing the renin-angiotensin-aldosterone system (RAAS) and vasopressin system. Several multicenter trials and meta-analyses show benefit by decreasing RRT and AKI. Data from seven systematic reviews showed a significant decrease of RRT rate associated with atrial natriuretic peptide (Number needed-to-treat, NNT = 22) and brain natriuretic peptide (NNT = 11), with no effect on mortality [34]. Hence, based on current data, use of natriuretic peptide, especially in high risk patients, may be considered.

Sodium Bicarbonate

It has been suggested that the use of sodium bicarbonate might be renoprotective [35]. A higher tubular pH could be protective by inhibiting the hydroxyl radical generation and lipid peroxidation. A multicentre RCT recruiting 427 patients in 2013 was negative [36]. More recently, a meta-analysis of three RCTs, with 877 patients, observed a benefit in a subgroup analysis of patients undergoing CABG (adjusted OR for RRT 0.38 [0.25–0.58] and OR for AKIN grade 3 0.45 [0.43–0.48]). However, imbalances in prognostically important characteristics were observed [37]. Hence, based on present data, prophylactic use of bicarbonate should not be considered.

Levosimendan

Levosimendan has predominant renal afferent vasodilatation, rather than efferent. It has been suggested that its use might be renoprotective. A meta-analysis of 13 RCTs with

1345 patients, of which 87.5% had left vetricular ejection fraction (LVEF) <40%, showed a reduction of AKI rate (OR 0.51, 95% CI 0.34–0.76) and AKI requiring RRT (OR 0.43, 95% CI 0.25–0.76), associated with the use of levosimendan [38]. A recent meta-analysis of 14 RCTs with 2243 patients [39], which included two recent large RCTs [40, 41], showed that levosimendan was associated with a significant reduction in 30-day mortality (RR = 0.71, 95% CI = 0.53–0.95; P = 0.023). Subgroup analysis showed that this benefit was confined to the moderate and low ejection fraction studies (RR = 0.44, 95% CI = 0.27–0.70; P < 0.001), whereas no benefit was observed in the preserved ejection fraction studies (RR = 1.06, 95% CI = 0.72–1.56; P = 0.78). Levosimendan also reduced the risk of RRT (RR = 0.66, 95% CI = 0.47–0.92; P = 0.015) and low cardiac output (RR = 0.40, 95% CI = 0.22–0.73; P = 0.003). Based on current data, levosimendan still may have a role if used preoperatively, especially for patients with LVEF < 30% and mainly CABG patients [42].

Dexmedetomidine

Dexmedetomidine is a highly selective alpha-2 agonist (ratio alpha-2 to alpha-1 1600:1) with short half-life. It inhibits renin release and attenuates sympathetic activity and vasoconstriction. It causes sympathetic stabilization, anti-inflammatory effect and ischemic/reperfusion injury attenuation. Data from an RCT of 200 patients, showed a significant AKI reduction rate (14% vs. 33%) associated with dexmedetomidine compared to placebo [43]. A retrospective single-center study of 1133 patients, using propensity score matching and logistic regression, observed an association between dexmedetomidine and a decrease in AKI rate (26.1% vs. 33.75%; adjusted OR 0.7; 95% CI 0.54–0.91, p = 0.008).

Vasopressin

Vasopressin binds to AVPR1a to promote vasoconstriction through several pathways, including modulation of adenosine triphosphate–sensitive K^+ channel function and nitric oxide production and enhancement of the vascular response to catecholamines. Since vasopressin acts on renal efferent arterioles, as opposed to noradrenaline which acts mainly on the renal afferent arteriole, might have nephroprotective effects. A double-blind RCT of 330 patients, in vasoplegic shock after cardiac surgery, showed a lower composite primary end-point (30-day mortality or stroke, AKI, mechanical ventilation >48 h, reoperation), with the use of vasopressin (32% vs. 49%, p = 0.0014) compared to norepinephrine. Use of vasopressin was also associated with less AKI (10.3% vs. 35.8%, adjusted OR 0.26, 95% CI 0.15–0.46, p < 0.0001), less atrial fibrillation (AF) with vasopressin (63.8% vs. 82.1%; P = 0.0004), no difference in digital or mesenteric ischemia and myocardial infarction [44]. Hence, based on current data, use of vasopressin to protect the kidney in patients with vasoplegic syndrome after cardiac surgery, should be considered.

Therefore, based on current data, the most promising pharmacological strategies are natriuretic peptide, dexmedetomidine and vasopressin.

Postoperative Strategies

KDIGO Bundle

Data from an RCT of 276 high risk patients showed that KDIGO bundle decreased AKI rate after cardiac surgery. KDIGO bundle consisted of avoiding ACE inhibitor/ARB for first 48 h postoperatively, avoiding hyperglycemia for first 72 h postoperatively, using alternatives to radiocontrast agents and lastly optimizing haemodynamics guided by PiCCO for first 48 h (consequently, more dobutamine and similar amount of fluid was used, compared to standard of care) [45].

Early Use of RRT

The early use of RRT after cardiac surgery has been suggested to be associated with improved in-hospital survival in patients with CSA-AKI. Data from a meta-analysis of 847 patients, including two RCTs and nine observational cohorts, showed a decrease of 28-days mortality associated with use of early RRT after cardiac surgery (OR 0.29, 95% CI 0.16–0.52, p < 0.0001) [46].

A recent well-designed single center RCT of 231 patients (50% of them were post cardiac surgery patients), showed that early use of RRT (within 8 h of diagnosis of KDIGO stage 2) was associated with a decrease in 90-day mortality (39.3% vs. 54.7%), a decrease in RRT duration, mechanical ventilation time and length of hospital stay and increase in rate of renal recovery by day 90 (53.6% vs. 38.7%), compared to late use of RRT after cardiac surgery (within 12 h of AKIN stage 3) [47]. Therefore, based on current data, use of early RRT should be considered.

Extended Daily Dialysis

KDIGO guidelines suggest the use of continuous renal replacement therapy (CRRT) in unstable patients (grade 2B). However, extended daily dialysis (EDD) may also be suitable for treatment in this setting. EDD provides hemodynamic tolerability and is significantly cheaper. No difference in renal function, mortality, renal recovery and hospital stay has been shown. Hemodynamic measurements, including heart rate, systolic blood pressure and diastolic blood pressure were comparable [48].

Early Detection of Acute Kidney Injury

The Role of Biomarkers

The use of serum and urinary biomarkers is an additional and promising new approach for the early diagnosis of CSA-AKI. However, the use of biomarkers remains more cumbersome than other diagnostic approaches and is not widely available. The serum creatinine level is traditionally used as a biomarker for renal impairment, but its usefulness can be affected not only by physiological processing (for example, urinary clearance of creatinine, or muscle mass) but also by drugs that block the tubular secretion of creatinine and by some underlying medical conditions, such as diabetes and liver disease [49].

Given the limitations of serum creatinine as a biomarker, there has been increasing interest in the last decade in the identification of new serum and urinary biomarkers for the early diagnosis and prognostication of AKI following cardiac surgery. New biomarkers could aid early diagnosis of AKI, even in the absence of concurrent renal dysfunction [50]. In response to ischaemic or nephrotoxic injury, tubular cell proteins are released into the urine. Thus, measurement of urinary biomarkers may be more specific and more sensitive than the measurement of serum biomarkers for the detection of AKI.

Novel biomarkers seem to improve risk stratification of CSA-AKI. However, the superiority of one biomarker over another, and the superiority of biomarkers over clinical models, are uncertain. At this stage, the use of biomarkers should not replace thorough clinical assessment of patients with AKI. Finally, the cost-effectiveness of using novel AKI biomarkers in clinical practice remains unclear [48].

Conclusion

AKI after cardiac surgery is a major perioperative complication that is associated with significant morbidity, mortality and increasing costs. Preventive strategies are limited and the evidence for most interventional therapies is as yet not substantial. As our understanding of the pathogenesis of AKI after cardiac surgery grows, we will be able to direct preventive and therapeutic strategies better. Current approaches include deferring elective surgery until there is adequate recovery following pre-existing renal injury, careful preoperative risk stratification of patients and consideration of less invasive procedures in those at greatest risk. Intraoperatively, the aim should be ‘haemodynamic optimization’ with goal-directed therapy that includes volume enhancement and judicious use of blood transfusion and inotropic support. We should attempt to avoid renal injury associated with prolonged aortic cross-clamping, prolonged CPB, intravascular haemolysis or contrast dye exposure. The most promising prospects for pharmacological renal protection appear to lie with atrial natriuretic peptide, vasopressin and dexmedetomidine but much more data are needed. Finally, prompt diagnosis of AKI by panels of biomarkers with early treatment using RRT may improve outcomes.

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Bleeding and Re-exploration After Cardiac Surgery

83

Xun Zhou, Cecillia Lui, and Glenn J. R. Whitman

High Yield Facts

- Laboratory tests such as hemoglobin, coagulation studies, fibrin levels, and thromboelastography should be used to guide the medical management of postoperative bleeding.
- In patients with asymptomatic anemia, a restrictive hemoglobin trigger of 7–8 g/dL should be used as the threshold for packed red blood cell (PRBC) transfusion.
- A 1:1:1 ratio of PRBCs, fresh frozen plasma, and platelets should be employed in patients with significant transfusion requirements.
- The use of isolated coagulation factor concentrates such as recombinant factor VII can be a useful adjunct in patients with refractory bleeding, but should be employed with caution through a standardized protocol.
- Timely surgical re-exploration can avoid the morbidity and complications associated with multiple blood transfusions.

Introduction

The Bleeding Academic Research Consortium (BARC) has defined significant coronary artery bypass graft-associated bleeding as chest tube output of greater than 2 L in 24 h, transfusion of 5 or more units of packed red blood cells (PRBCs) in 48 h, intracranial hemorrhage, or need for surgical exploration or death [1]. Ideally, postoperative bleeding should be recognized and addressed before any of these endpoints are reached. Minimizing the morbidity and mortality associated with bleeding in cardiac surgery requires a coordinated management strategy, as there are preoperative, intraoperative, and postoperative factors which increase the risk of bleeding in cardiac surgical patients. A critical component of managing bleeding is the judicious use of blood products. While transfusion can play an important role in improving oxygen delivery, hemodynamics, and hemostasis, studies have demonstrated that inappropriate use of blood products can increase morbidity, mortality, length of stay, and the cost of care. It is necessary to keep in mind that blood transfusions represent only one tool in the clinician's armamentarium for addressing postoperative bleeding, which extends from preoperative preparation to meticulous intraoperative technique to postoperative management, including surgical re-exploration.

Risk Factors for Bleeding Associated with Cardiac Surgery

In addition to any pre-existing and underlying coagulopathies, cardiac surgical patients can have multiple etiologies of acquired coagulopathy. Urgent coronary revascularization patients have often received a loading dose of antiplatelet agents such as clopidogrel and ticagrelor prior to undergoing coronary angiography. If possible, surgery should be delayed to allow these agents to wash out. An analysis of the SWEDEHEART registry demonstrated that the risk of bleeding associated with clopidogrel reaches that of the population at large after 5 days of discontinuation, while with ticagrelor, the washout period is only 3 days [2]. In patients requiring urgent revascularization who cannot wait the recommended washout period, intraoperative platelet transfusion and careful postoperative monitoring is warranted. Routine prophylactic platelet transfusion in this patient population is currently not endorsed by the American Association of Blood Banks (AABB), citing a lack of evidence [3]. Nonetheless, platelet dysfunction in this population occurs and should be taken into account when considering timing of surgery and the need for platelet transfusions postoperatively.

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Patients presenting with an acute coronary syndrome will likely be on a continuous infusion of unfractionated heparin. This can be paused to allow for a cleaner sternotomy, mammary, radial, or vein graft dissection, and institution of cardiopulmonary bypass (CPB). However, the risk of discontinuing heparin should be weighed in the context of the severity and acuity of any coronary lesions. Prophylactic subcutaneous heparin should be held at least 6 h prior to surgery. Similarly, patients on long-standing anticoagulation with warfarin or a novel oral anticoagulant should be transitioned to a heparin infusion and await normalization of coagulation prior to surgery. Despite a manageable half-life, the use of low-molecular-weight heparin should be avoided if possible, as studies have suggested that these agents may be associated with increased risk of major cardiovascular or cerebral adverse events when used as a bridging strategy [4]. Multiple studies have demonstrated that the benefits of continuing aspirin peri-operatively outweigh the slightly increased risk of bleeding [5].

CPB requires high levels of systemic anticoagulation with heparin, but this should be reversed with protamine prior to chest closure and arrival to the intensive care unit. However, it is important for postoperative care providers to ensure that the activated coagulation time (ACT) has returned to normal limits. Protein-bound heparin may not be adequately reversed by the initial protamine bolus, and although the intraoperative ACT may have normalized, "rebound" may occur when previously bound heparin returns to circulation and can lead to clinically important anticoagulation [6]. The phenomenon will be readily diagnosed by repeating coagulation studies with and without heparinase and treating with an additional dose of protamine as necessary.

The CPB circuit also has well-described effects on the body's hemostatic ability and has been shown to both dilute and consume coagulation factors, induce fibrinolysis, and diminish the quantity and function of platelets [7]. While these effects are transient and vary in severity from patient-to-patient, it is important to perform a thorough assessment of all aspects of the coagulation cascade in patients with ongoing bleeding, as derangements can occur at multiple levels following cardiac surgery.

Medical Management of Postoperative Bleeding

The medical management of postoperative bleeding following cardiac surgery consists of correction of coagulopathies guided by appropriate testing. However, the importance of rewarming and the correction of hypoperfusion and acidosis should not be overlooked. Hypothermia and acidosis both can cause coagulopathy in patients who otherwise would have no derangements in their hemostatic function and should be quickly addressed with active warming and sodium bicarbonate as necessary. Despite the fact that many patients may need inotropes to assure an adequate cardiac output and end-organ perfusion, vasodilators may be necessary in hypertensive patients to reduce the risk of bleeding. Finally, small amounts of positive end-expiratory pressure (PEEP), perhaps 10 cm, may be useful in tamponading minor sources of mediastinal bleeding [8]. In the early postoperative period, both bleeding and the systemic inflammatory response can cause patients to be volume-responsive, and fluid resuscitation with crystalloid may be an appropriate initial step. However, if bleeding persists, crystalloid resuscitation may further dilute present clotting factors, and repeat testing and/or prophylactic plasma and cryoprecipitate may be necessary.

Patients with elevated activated partial thromboplastin time (aPTT) or prothrombin time (PT) suggestive of coagulation factor deficiency/dysfunction should receive fresh frozen plasma (FFP). Actively bleeding patients with thrombocytopenia or suspected/known platelet dysfunction should receive platelet transfusion. The need for cryoprecipitate can be reflected by an elevated thrombin time or, in facilities that can rapidly process it, a low fibrinogen level. Desmopressin (ddAVP) promotes the release of von Willebrand factor (vWF) and can be given to patients who may have vWF deficiency or uremic platelet dysfunction. It has also been proposed as an adjunctive measure to treat coagulopathic bleeding following CPB after showing initial promise in small prospective trials in the 1980s [9]. However, a recent multicenter randomized controlled trial demonstrated no benefit, potentially as a result of improvements in the intraoperative management of coagulopathies [10].

Thromboelastography (TEG) has emerged as a useful intraoperative and bedside tool for assessing coagulopathies [11]. In small, prospective studies, it has been found to reduce the quantity of blood products transfused following cardiac surgery [12, 13]. By quantifying the visco-elastic properties of blood, TEG is capable of distinguishing coagulation factor deficiencies, fibrinogen deficiency, and platelet deficiency/dysfunction in a single assay that can be run at the point of care. While point-of-care testing has not been shown to be superior to assays run in a centralized laboratory, both are superior to the use of clinical judgment alone without laboratory value adjuncts [14].

While blood products are an essential and irreplaceable component of the resuscitation of patients with significant bleeding, numerous studies have highlighted the risks associated with transfusion [15, 16]. In addition to transfusion reactions and potential transmission of bloodborne infections, allogeneic blood is inherently immunomodulatory [17], and PRBC transfusions have been shown to increase the risk of postoperative nosocomial infections [18] and venous thromboembolic events [19]. While the effects of transfusion of platelets, plasma, and other products is less well studied and understood, the putative mechanisms for increased morbidity remain the same [20, 21].

Guidelines for red blood cell transfusion in asymptomatic anemic patients are becoming well-established. The recent TRICS III trial of approximately 5000 randomized patients and TITRe2 trial of over 2000 randomized patients demonstrated that a hemoglobin transfusion threshold of 7.5–8 g/dL in routine open heart surgery is not inferior to a more liberal transfusion trigger when used as the sole indication for transfusion [22–24]. In these large multicenter randomized controlled trials, which included both elective and urgent patients, the restrictive transfusion strategy fared no worse than triggers of 9–9.5 g/dL [25]. The AABB guidelines support the use of a restrictive hemoglobin transfusion threshold and further recommends the transfusion of only 1 unit of PRBCs rather than 2 before re-checking the hemoglobin [26].

In patients with significant ongoing transfusion requirements, it is important to balance the administration of PRBCs with other blood products. Unbalanced red cell transfusions can result in worsening coagulopathy if clotting factors and platelets are lost but not replaced. Fresh frozen plasma (FFP) can be used to replenish both volume and coagulation factors, while prothrombin complex concentrate (PCC) provides a similar milieu in a much smaller volume. In several institutional series, PCC has been associated with less blood loss and need for PRBC transfusion than FFP [27, 28]. However, in patients with factor deficiencies, FFP should be considered first-line over PCC, which may be associated with an increased risk of acute kidney injury in the cardiac surgical postoperative population [28].

The use of massive transfusion protocols (MTP) can help to expedite and ensure that balanced ratios of blood products are administered. While triggers for these protocols can vary by institution and allow for activation at a provider's discretion, serious consideration for a standardized approach should be given once more than 10 units of PRBCs have been transfused [29]. A recent large, multicenter trial found that a 1:1:1 ratio of PRBCs, FFP, and platelets resulted in better hemostasis than a 2:1:1 transfusion strategy [30].

Additional new plasma-derived or recombinant coagulation factor products are entering the market but should be considered with caution and not employed routinely. The best studied of these products is recombinant factor VII (rFVIIa), which has been associated with a trend towards increased rates of stroke and thrombotic complications, although these did not reach statistical significance in the initial phase II trial [31]. However, when administered in low doses, these risks may be ameliorated and outweighed in patients with refractory coagulopathic bleeding [32]. Ideally, these products should be used as part of a concerted collaboration between the surgeons, intensivists, and hematologists caring for the patient. Establishing institutional guidelines and policies regarding their use can help to standardize and expedite their application, limiting risk and expense.

Since CPB induces hyper-fibrinolysis, a number of antifibrinolytic agents have been studied and employed in the perioperative management of cardiac surgical patients. While initially popular, following the Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART), aprotinin is no longer widely used in cardiac surgery. While it was associated with significantly decreased bleeding in high risk patients, it greatly increased the risk of renal failure, heart failure, and thrombotic complications when compared to tranexamic acid (TXA) and epsilon aminocaproic acid [33]. Currently, the Society of Thoracic Surgeons and Society of Cardiovascular Anesthesiologists guidelines do not recommend the routine use of aprotinin for blood conservation, but acknowledge that it may still have a role in high risk patients such as Jehovah's Witnesses [34]. TXA and epsilon aminocaproic acid are well recognized as safe antifibrinolytics with beneficial effects on postoperative bleeding after cardiac surgery [35].

Surgical Methods to Manage Postoperative Bleeding

If all medical strategies are exhausted in the management of postoperative bleeding, one should consider a surgical cause underlying any persistently excessive bleeding. Reoperation for bleeding occurs in anywhere between 2.2% and 11.6% of the seven most commonly performed adult cardiac surgical procedures as reported by the Society of Thoracic Surgeons National Report [36]. Patients requiring reoperation for excessive bleeding are at a significantly higher risk for mortality and major morbidity including stroke, need for intra-aortic balloon pump, acute renal failure, sternal wound infection, and prolonged mechanical ventilation [37–41].

In a large series of 18,891 patients undergoing coronary artery bypass grafting and/or a valve procedure from 2000 to 2010 at the Cleveland Clinic, 566 (3%) patients required reoperation for excessive bleeding. Patients undergoing reoperation for bleeding had a significantly higher rate of mortality, 8.5% compared to 1.8% in propensity-matched controls that did not undergo reoperation. In their series, 74% of reoperations were attributed to technical factors, 13% to coagulopathy, 10% to both technical factors and coagulopathy, and 3.3% due to other reasons [42]. These statistics are similar to other series, which have demonstrated an identifiable surgical source of bleeding in anywhere from 67% to 82% of reoperations for bleeding [43]. In the series of 2898 patients described by Karthik et al., the identified sites of bleeding included: graft/anastomoses (57.5%), sternum/LIMA bed (31.5%), extrapericardial sites (8.2%), and cannulation sites (2.8%) [44]. Interestingly, multiple studies attempting to identify risk factors for reoperation for bleeding have been unable or rarely able to find significant predictors [39, 45]. These findings are consistent with the hypothesis that reoperation for bleeding is generally due to technical failures, and less dependent on patients' preoperative risk factors.

Timing of Re-exploration

As outlined above, the data clearly show that reoperation for bleeding is a complication that is associated with significant morbidity and mortality. As a result, many surgeons have been less motivated to take patients back to the operating room until all potential medical sources of bleeding are ruled out or corrected. While it is appropriate to correct potential medical coagulopathies before considering re-exploration, delay in returning to the operating room may also lead to increased risk of morbidity and mortality. In a study by Choong et al. in 2007, of 3229 CABG patients, 157/191 were re-explored within 12 h of surgery, and 34/191 were explored greater than 12 h after the index surgery was completed. In the under 12 h group, patients had a shorter ICU stay (median 3 days vs. 8.5 days), less IABP support (22.3% vs. 44.1%), and lower mortality (7% vs. 29.4% p = 0.001) [46]. These findings were consistent with a prior study showing significantly higher rate of adverse outcomes in patients who waited more than 12 h to return to the operating room [44].

Reoperation Versus Transfusion

During the correction of postoperative medical coagulopathy, patients are hemodynamically supported with transfusion of blood products and crystalloid solutions. However, transfusion of blood products and specifically PRBCs is not benign. Several studies have shown that PRBC transfusion is associated with increased risk of morbidity and mortality, including major infections including deep sternal wound infections, pneumonias and blood stream infections [18, 47]. A study by Whitson et al. found that the risk for the majority of the infectious complication associated with blood product transfusions occurred if the patient had been transfused over 5.5 units of any type of blood products on average [48]. In a retrospective study of a propensity matched group of 232 patients requiring surgical re-exploration requiring CPB, Ranucci and colleagues found that each unit of PRBCs transfused conferred a 0.25% increase in the risk for mortality [49].

Thus, both re-exploration for bleeding and transfusion of packed red blood cells are independently associated with significant morbidity and increased risk of mortality. As shown by Vivacqua et al. in his retrospective examination of 18,891 patients undergoing coronary artery bypass grafting, valve or combined operations between 2000 and 2010, he identified 566 patients (3%) who underwent reoperation for bleeding. After propensity score matching for potential confounding variables including intraoperative transfusion of packed red blood cells, fresh frozen plasma and platelets, he found that hospital mortality was significantly higher for patients undergoing reoperation, 8.5% compared to 1.0% for those patients who did not undergo a reoperation. Furthermore, patients who received blood and underwent reoperation had a higher mortality than those receiving blood but without undergoing reoperation (8.7% compared to 6.6%) [42]. One might take away the message that blood transfusions are morbid, but blood transfusion with reoperation convey even more morbidity. The problem is that there are only a few propensity matched studies suggesting this, with no head to head comparisons.

Apart from being intrinsically interesting, and a dilemma surgeons face almost daily in the postop management of open heart surgery patients, currently in the United States the National Quality Forum and the Society of Thoracic Surgery regard reoperation for bleeding as a quality measure but not transfusion exposures [36]. Thus, surgeons are incentivized to treat postoperative bleeding medically, exposing their patients to transfusion risks, while delaying reoperation, with the hopes that transfusions and tincture of time will solve the problem. True, this practice spares patients a reoperation, which is acknowledged as morbid, and avoids a quality demerit for their program. However, it is unclear whether this behavior is wise, as unquestionably, those that undergo reoperation will have received more transfusions as a result of the delay to see if the bleeding will stop just with transfusions, compared to having gone back for an exploration earlier. Our current model advocates for late re-explorations with the increase in transfusion exposures that that allows. This dual exposure, transfusions and reoperation, Whitson suggests, is worse than fewer transfusions and an earlier reoperation [48]. Thus, the surgeon must weigh not only the risks of multiple transfusions against the risk of re-exploration, but the consequence of reoperation, but not transfusions, on the program's assessed quality.

Intraoperative Approaches

Of note, there are intraoperative alternatives being explored to decrease the rate of postoperative bleeding. A randomized control trial from Rousou et al. in 1989 randomized 333 patients from 11 centers in the US to receive either fibrin sealant or topical hemostastic agent intraoperatively when bleeding was noted. There was a 92.6% success rate in controlling bleeding within 5 min of application reported for the fibrin sealant compared to 12.4% for conventional hemostatic agents. While there was no difference in mortality or length of stay between patients in the fibrin sealant group compared to the topical hemostatic agent group, it was noted that patients in the fibrin sealant group experienced significantly less high volume postoperative bleeding and had a significantly lower rate of reoperation for bleeding (5.6% compared to 10%, p = 0.0089) [50].

A planned delayed sternal closure has always been an option for patients who experience significant medical coagulopathy while in the operating room, with reported survival rates from 66% to 81.4% [51, 52]. Another alternative being explored more recently is the use of a vacuum assisted closure (VAC) system for patients who would normally be packed and left with an open chest. In a study by Fleck et al. in 2008, the preliminary experience using VAC system for delayed sternal closure was reported. A total of 22 patients had delayed sternal closure managed with a VAC device during what otherwise would have been an "open chest" period of time. There were no increased deep sternal infections and no VAC system complications. The use of the VAC demonstrated no negative hemodynamic or respiratory effects, and was able to stabilize the thoracic cage making movement and mobilization of the patient easier for nursing staff [53]. Furthermore, at the 2018 annual meeting for the American Association for Thoracic Surgery, the results of using negative pressure wound therapy (NPWT) to manage post cardiotomy open chests in 588 patients at the Cleveland Clinic was presented. The use of NPWT was associated with lower in-hospital mortality (39% compared to the 51% in the traditionally managed open chest patients), less mediastinitis (1.4% compared to 5.2%), and lower rates of sepsis (12% versus 24%) [54]. These findings highlight the high mortality and morbidity associated with postoperative bleeding as well as the use of NPWT as a potential management strategy for open chest patients.

Conclusion

Post-operative bleeding requiring surgical re-exploration is a frequent complication following cardiac surgery. Re-exploration for bleeding is associated with increased operative mortality and morbidity after cardiac surgery. Despite the multitude of factors that contribute to worse outcomes, there is an inherent risk for worse outcomes due to the second operation itself. The interplay between time to re-exploration for bleeding and volume bled before take back must be taken in the context of the patient's clinical picture and no one factor should be relied upon. Understanding which patients are at risk for post-operative bleeding will help guide future practice and mitigate worse outcomes associated with post-operative bleeding.

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Sternal Wound Infections

Tomas Gudbjartsson

High Yield Facts

- Surgical site infections (SSIs) are common complications after open heart surgery.
- The knowledge of SSIs following open heart surgery has increased over the last decade and much is known about the pathogenesis, prevention and treatment.
- Although most of them are superficial and respond to minor wound debridement and antibiotics, 0.25–5% of patients have deep sternal wound infection (DSWI) that can be fatal.
- Most of the infections are detected within days or weeks after surgery but late infections with sternocutaneous fistulas are encountered less often and represent a complex surgical problem.
- The most common pathogens in DSWI are coagulase-negative staphylococci (CoNS), followed by Staphylococcus aureus and Gram-negative bacteria.
- These infections are usually detected after purulent discharge from the wound, fever, or following sternal dehiscence or mediastinal widening on chest X-ray with or without sepsis and organisms cultured from blood or mediastinal tissue and fluid.
- Numerous risk factors have been identified with diabetes mellitus, obesity, peripheral arterial disease, chronic renal failure and smoking with chronic pulmonary disease being the most important ones.
- The identification of risk factors is crucial to prevent SSIs, as is the application of best and up-to date preventive measures.
- First line of treatment consists of intravenous antibiotics, commonly vancomycin, until results from antimicrobial susceptibility tests are available.
- For DSWI surgical treatment is necessary and usually starts with debridement of the wound with several surgical approaches available.
- In recent years negative-pressure wound therapy (NPWT) has gained popularity.
- Using state of the art techniques, including NPWT, early mortality due to SSIs is close to none, although long-term survival may still be affected.

Introduction

Surgical site infections (SSIs) following cardiac surgery are either of the sternotomy wound or the leg due to vein harvesting for coronary artery bypass grafting (CABG); most of them being diagnosed in the first month after surgery. Some SSIs, however, can be diagnosed months or even years after surgery; such as chronic sternocutaneous fistulas. Modern care of sternal SSIs following open heart surgery involves effective primary prevention and eradication of infections with low rate of sequelae.

Clinical Presentation

Together with atrial fibrillation, kidney injury and perioperative bleeding, SSIs are among the most important complications related to open heart surgery and often result in significant morbidity including mortality and increased cost of treatment. The reported incidence of sternal SSIs is up to 9.7%. Fortunately most sternal SSIs are superficial and respond to minor wound debridement and antibiotics. However, 0.25–5% patients develop deep sternal wound

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infections (DSWIs), which can have severe consequences including increased mortality, morbidity and costs [1].

Sternal wound infections can be divided into *superficial* infections and *deep* infections, based on the depth of the infection in the wound; the deeper ones reaching under the sternum and into the anterior mediastinum (Fig. 84.1a). Thus, a DSWI may manifest as postoperative mediastinitis, which usually presents *early* in the first few weeks postoperatively but in rare cases can present as a subacute *late* infection such as osteomyelitis, subcutaneous abscess, and sternocutaneous fistulas [2].

According to the definition by Centres for Disease Control and Prevention (CDC) an *early superficial* infection occurs within 30 days of the operative procedure and involves only the skin and subcutaneous tissues of the incision. In addition, the patient must have at least one of the following: (1) purulent drainage from the superficial incision, (2) organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision, (3) at least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat and superficial incision is deliberately opened by the surgeon, unless incision is culture-negative, and/or (4) diagnosis of superficial incisional SSI made by the surgeon or attending physician.

A DSWI is specifically defined as an infection that reaches the mediastinum, which means it reaches under the sternum.

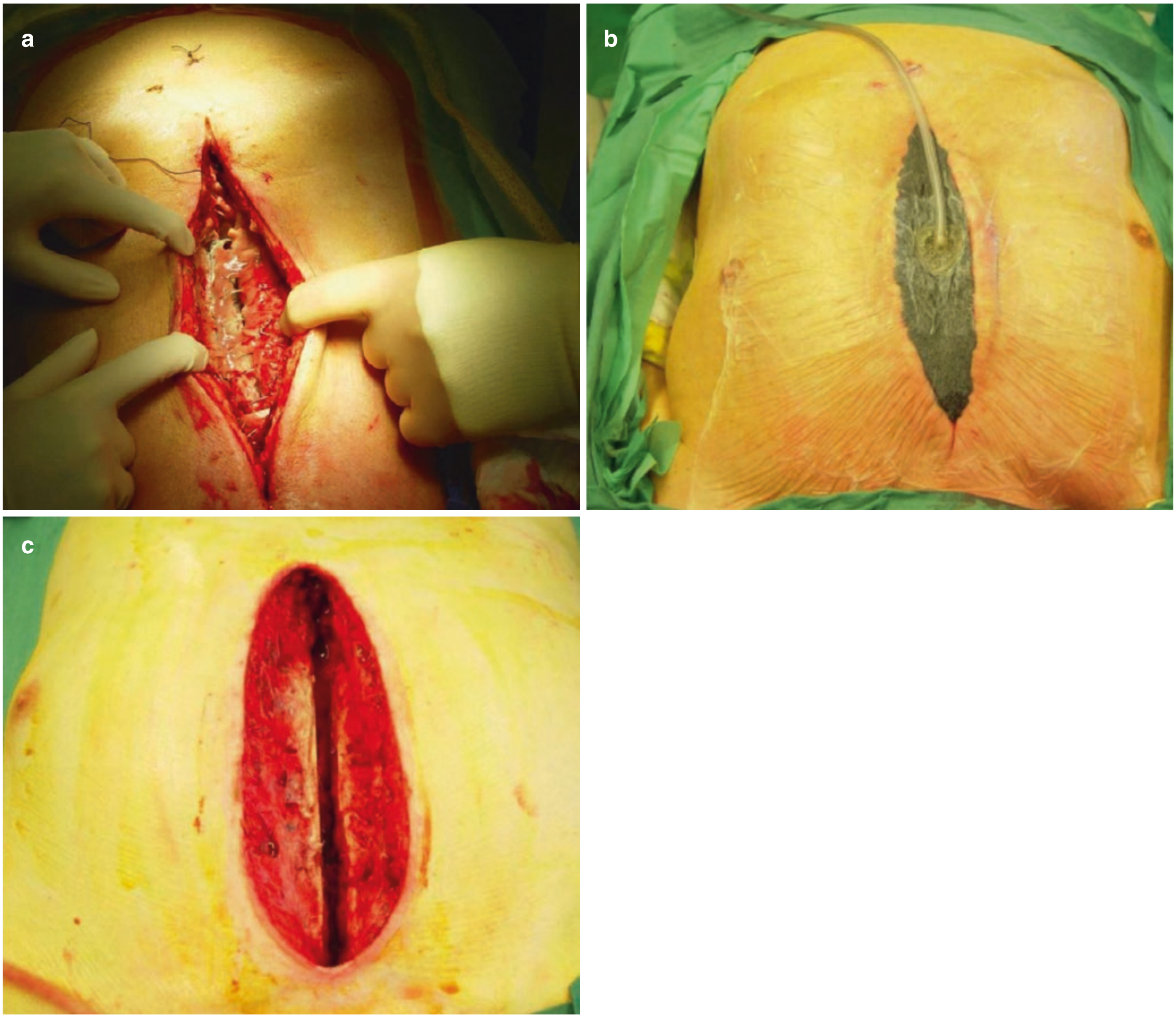

Fig. 84.1 Purulent deep sternal wound infected detected 1 week after surgery. (**a**) The sternal wires are still in place. (**b**) The wound after application of negative pressure wound therapy and (**c**) 1 week later. See text for details. (Photos: Tomas Gudbjartsson. Published with the courtesy of the Icelandic Medical Journal)

Table 84.1 CDC criteria for the diagnosis of deep sternal wound infection[a]

1.	Organisms cultured from mediastinal tissue or fluid obtained during a surgical operation or needle aspiration
2.	Evidence of mediastinitis seen during a surgical operation or histopathological examination
3.	At least one of the following signs or symptoms with no other recognized cause: fever (>38 °C), chest pain, or sternal instability and at least one of the following:
	(a) purulent discharge from mediastinal area
	(b) organisms cultured from blood, or discharge from mediastinal area
	(c) mediastinal widening on X-ray

[a] Horan et al. (2008) [2]

According to the definition by CDC the diagnosis of postoperative mediastinitis requires at least one of the three criteria given in Table 84.1 [2].

The definition of *late* sternal SSI is less well defined than that for early infections and there is a large overlap among the various types of infections, including osteomyelitis, subcutaneous abscesses, and chondritis [3]. Sternocutaneous fistula belongs to this group of late infections and is defined as a draining sinus tract from the sternum to the skin, with an apparently healed sternotomy wound, treated surgically after discharge from hospital.

Pathogenesis

Coagulase-negative staphylococci (CoNS), mostly *Staphylococcus epidermidis*, are the most commonly reported pathogenic agents associated with SSIs following open heart surgery, followed by the previously dominating bacterial agents *Staphylococcus aureus* and Gram-negative bacteria. Less commonly reported agents include streptococci, anaerobic bacteria such as *Propionibacterium acnes*, *Candida albicans*, Aspergillus and *Mycobacterium tuberculosis* [3].

CoNS belong to the normal flora of the skin and do not cause harm unless there is a breach in the integrity of the skin [4]. Although many subtypes of CoNS have been identified in humans, only a few have been reported to cause disease, the most well-known being *S. epidermidis*. CoNS are commonly found in the sternal wound before closure and may originate from the patient's own skin as well as from airborne external contamination during surgery. Mediastinitis caused by CoNS has been reported to be associated with diabetes mellitus, obesity, chronic obstructive pulmonary disease (COPD) and typically presents at least 10–14 days postoperatively, often with sternal dehiscence in combination with only moderate increase in C-reactive protein (CRP) levels.

S. aureus is mainly found in the anterior nares of humans, with around 20% of all people being persistent carriers and nasal carriers have increased risk for sternal SSIs [5]. *S. aureus* does not, however, belong to the normal commensal bacteria of the skin on the sternum. Sternal SSIs caused by *S. aureus* are considered to be caused by intraoperative contamination of the wound, although they often present 2–4 weeks after surgery or even later.

Gram-negative bacteria do not constitute part of the normal skin flora nor are present in the air of operating rooms, and are probably caused by contamination or haematogenous spread from other sites during the postoperative period [6]. These sternal SSIs often show a fulminant course with high CRP levels, sepsis and high mortality and complication rates. Most deep Gram-negative deep sternal SSIs present early (within 1–2 weeks) after surgery.

P. acnes is an increasingly recognized pathogen, formerly usually regarded as a harmless contaminant. However, *P. acnes* has been proposed to have a role in postoperative sternal SSI. *P. acnes* is regularly not detected in routine bacterial wound samples unless specifically looked for, since specific anaerobic culture techniques are required and longer time to grow in the laboratory.

Incidence and Risk Factors

The incidence of DSWI is most often reported to be in the 1–3% range; however, the rates vary considerably (or from 0.25% to 5%) due to different patient populations and diagnostic criteria [3, 7–9].

Superficial sternal wound infections have not been studied as thoroughly as deep infections, due to their much lower morbidity and mortality. The incidence is higher than for deep sternal SSIs, and in prospective studies lies in the 2–6% range. These infections are often minor and respond to oral antibiotics or minor wound revision. Risk factors include those for other SSI, including advanced age and obesity.

A diagnosis of sternal SSI is most often established in the first days or weeks after the primary operation [1]. Numerous risk factors have been identified; especially for DSWIs. These can be divided into three categories: (a) Preoperative: diabetes mellitus, obesity, peripheral arterial disease, smoking, low left ventricle ejection fraction, chronic renal failure, COPD. (b) Perioperative: bilateral use of internal mammary arteries (BIMAs). (c) Postoperative: longer ventilator support, use of β-adrenergic drugs.

Following the introduction of continuous infusion of insulin during open-heart surgery, the importance of diabetes mellitus as an independent risk factor for deep sternal SSI has diminished. Furthermore, the role of gender as a risk factor for deep sternal SSI is unclear, but female sex has been reported to be associated with increased risk.

Although the use of BIMAs has been shown to improve long-term survival for CABG patients, this strategy has long been considered a risk factor for DSWI when compared to the use of a single left internal mammary artery (LIMA). This is thought to be related to decreased vascularity of the sternum following BIMA harvesting. In a large meta-analysis by Dai et al. [10], the use of BIMA was shown to increase the relative risk of DSWI by 62% when compared to LIMA. This increased risk was most prominent in patients with diabetes and in the group of elderly. The association of the use of BIMA and DSWI was recently challenged in a study with over 1.5 million CABG patients where the use of BIMA was not an independent risk factor for DSWI except in patients with chronic complications of diabetes mellitus [11].

Several other risk factors for DSWI have been identified and often they can be related to the mechanisms by which they promote infection, such as the mechanical force to the wound (e.g. cough related to COPD, re-exploration for bleeding), reduced circulation in the wound (e.g. peripheral arterial disease, diabetes mellitus, smoking etc.), haematogenous spread (e.g. renal failure) and reduced host immunity (e.g. systematic corticosteroids) [3].

Treatment

Once diagnosed, sternal SSI is initially treated with intravenous antibiotics, usually before microbiological identification and antibiotic susceptibility are established. While awaiting results of these tests and as CoNS are often multiresistant and methicillin-resistant staphylococcus aureus (MRSA) common in some centres, first-line antibiotic treatment is commonly intravenous vancomycin [7]. However, when infection with either *S. aureus* or CoNS has been established, cloxacillin or other β-lactamase antibiotics are commonly used [3].

In addition to antimicrobial therapy, surgical treatment is generally necessary for DSWI. The most appropriate surgical approach for the treatment is still debated, but wound debridement is always necessary. To close the wound usually two approaches are used; either primary closure, i.e. the wound is closed by drawing the wound edges together, or delayed primary closure, where the wound is debrided and left open for treatment and observation, and then closed a few days later. By using either of these approaches, the sternal halves can often be re-wired in a fashion similar to that in a primary operation—or using the more secure Robicsek-technique if there is risk of fracture of the bone.

After revision of the wound, either closed irrigation or more commonly open wound dressings that involve frequent changes of paraffin gauzes and close observation of the wound is a common practice. For the closed approach, however, antibiotic irrigation can be added as an adjunct therapy [12].

Regardless of the treatment method stability of the sternum before delayed primary closure is of great importance, as cases of injuries to the anterior surface of the heart from sternal spurs have been reported. Furthermore, patients with unstable sternum and open wound often have impaired pulmonary function that can require prolonged mechanical ventilation. If a delayed closure of the wound is chosen a titanium plate can be used to fix the unstable sternum, provided the wound is clean. In some cases, however, the plates have to be removed due to infection.

Occasionally a soft tissue flap transposition is required to fill a sternal defect resulting from repeated interventions or after extensive debridement such as when a subtotal sternectomy is required to eradicate the infection. In such cases highly vascularized greater omentum can be used as a soft tissue flap [13] and the wound then later closed by delayed primary intention.

More often, however, a muscle flap is used to fill up the sternal defect, usually the pectoralis muscle or in some cases the rectus abdominis muscle. A problem following sternal reconstruction using muscle flaps, however, is chronic pain and/or sternal instability [14].

There is no consensus regarding the timing for surgical reconstruction or about the necessity for obtaining negative cultures at the time of closure [15].

Negative-Pressure Wound Therapy

Negative-pressure wound therapy (NPWT), is a newer treatment modality that can stabilize the sternum and promote granulation of the wound. Since it was first used for the treatment of DSWI in 1999 [16], numerous reports have been published that show its usefulness in these complex infections.

In brief NPWT promotes wound healing through removal of debris and excess fluids by creating negative pressure, or vacuum, in a well-sealed wound. NPWT is believed to aid wound healing in numerous ways with increased granulation tissue formation, perfusion to the wound edges together with removal of fluid being the most important. This promotion of wound healing is believed to involve modulation of cytokines with an anti-inflammatory profile together with mechanoreceptor and chemoreceptor-mediated cell signalling. The net result is deposition of granulation tissue, angiogenesis and extracellular matrix remodelling.

There are four separate elements in a NPWT device: (a) a pump that generates negative pressure within a tightly sealed wound, (b) dressing materials that both fill the wound (usually polyurethane foam) and cover it (adhesive drape), (c) non-collapsible tubing that removes fluid from the wound, and (d) a container to collect the fluid and debris that are removed from the wound by the vacuum created in the system. Today a number of different commercially available NPWT systems are available.

The use of NPWT for DSWI is shown in Fig. 84.1a–c. Most often the negative pressure in a sternal wound is applied at a continuous pressure of −125 mmHg, but lower pressures can also be used at the expense of more pronounced diastasis of the foam [17–19].

After 2–4 days treatment with vacuum the wound is usually reopened. The decision to close the wound usually depends on clinical observation during wound debridement but also infection-related laboratory findings such as leucocyte counts and especially CRP levels, and multiple negative tissue cultures [3]. Otherwise, a new foam is placed with negative pressure. Most often DSWI patients require 2–4 dressing changes as part of their treatment with NPWT before the wound is healed and can be closed (Fig. 84.1c) [20]. This delayed primary closure approach with re-wiring of the sternum and suture of the skin is achieved in most cases [21]. A few reports have described the rare use of NPWT for secondary closure of the wound, but this approach generally shows worse outcome.

Complications related to NPWT when used for sternal SSIs are usually minor; most often pain at the edges of the wound or light bleeding upon removal of the foam. However, major bleeding has been reported and is a potentially fatal complication of NPWT. This is usually seen when the sponge dressings are changed or when negative suction is introduced to the sponge, resulting in displacement of the heart towards the thoracic wall and possible contact of the right ventricle with the edge of the sternum. However, a recent large series demonstrated very few major bleedings when using the proper technique of NPWT [20].

Outcome of Treatment

Historically and before the introduction of more advanced surgical techniques, the mortality of DSWI ranged between 20% and 45% [22]. This is in contrast to contemporary reports where the mortality usually lies between 1% and 14% [20, 23, 24]. Most of these patients require lengthy hospitalizations and undergo numerous surgical procedures to eradicate the infection. In comparison to patients without sternal infections they still do not have improved quality of life after surgery.

Furthermore, long-term outcome of these patients is also negatively associated with DSWI with long-term study showing almost doubled adjusted hazard ratio for all-cause mortality at 10 years after the primary operation. DSWI also increase the risk of late chronic infections.

Both improved sternal stabilization and earlier mobilization of patients are already established advantages of NPWT. Still the superiority of NPWT over conventional techniques has been questioned for the treatment of DSWI, and there is definitely a need for more randomized controlled trials. Despite this lack of evidence, currently many institutions prefer NPWT for the treatment of sternal SSIs [3].

The overall cost of sternal SSI treatment is generally no higher when NPWT is used rather than conventional treatment. In a Swedish study from 2008 the total cost of treatment was shown to be 2.5 times higher for cases treated with NPWT than for non-SSI patients, which was similar to conventional treatment. Although the material cost is often greater using NPWT, it is less laborious, as the wound is only changed two or three times a week, resulting in similar or even reduced total cost [24]. Still, however, randomized studies are lacking that could prove that NPWT is economically superior to other techniques used for sternal SSIs.

Late Sternal Wound Infections

Late infections following open heart surgery have not received much attention, and most reports have been case studies. However, in two studies, one of them nationwide, the incidence was around 0.26% [25, 26]. They most commonly involve sternocutaneous fistula, an abnormal passage or communication between the sternum and the surface of the skin (Fig. 84.2). The time to first intervention ranges from a few weeks up to months and even years and Gram positive cocci have been shown to be most common, followed by Gram-negative bacteria and *C. albicans*

In case series previous treatment for DSWI, advanced age and history of previous cardiac operations have been shown to be associated with sternocutaneous fistulas [27, 28]. Furthermore, a case control study found that treatment for

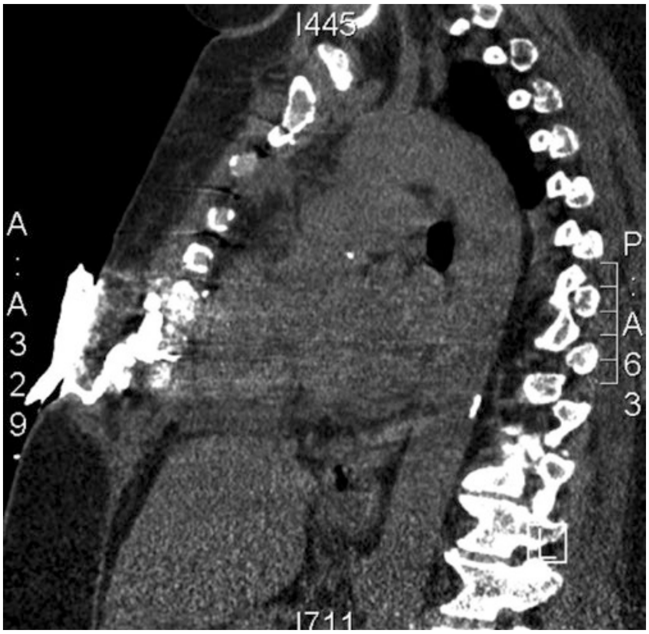

Fig. 84.2 Fistulography showing a subcutanous fistula in the lower sternum. (Published with the courtesy of the Scandinavian Cardiovascular Journal)

early sternal SSI, renal failure, history of smoking and the use of bone wax were strong independent risk factors for sternocutaneous fistulas [25]. In a porcine model bone wax was shown to both inhibit bone healing and induce chronic inflammation in sternal wounds. Foreign objects could also play a role, although sternocutaneous fistulas are not common following sternal reconstructions where titanium plates are used [29].

Treatment of sternocutaneous fistulas most often entails numerous surgical interventions and prolonged antibiotic treatment. In some cases infections associated with sternocutaneous fistulas can be treated adequately with antibiotics alone, but most patients require surgical treatment to eradicate the infection [25, 26, 30].

Conventional surgical treatment of sternocutaneous involves debridement with removal of infected wires and then closure of the wound. Traditionally, in long-standing sternocutaneous fistulas a radical excision of parts of the sternum may be needed to eradicate the underlying infection, followed by soft tissue flap surgery to fill up the sternal defect. Despite the combination of adequate antibiotic therapy with conventional surgical treatment and NPWT sternocutaneous fistulas can become a recurrent problem [25]. Persistent sternocutaneous fistula reduces the patient's quality of life due to chronic leakage from the wound. The short term mortality has been shown to be increased as well long term survival with 58% being alive at 5 years compared to 85% in a control group [25].

Preventive Measures

SSIs may result from contamination during surgery, both from the surgeon or more commonly the patient. Blood-borne infections can also spread to the surgical wound and in rare instances infections from adjacent structures, such as iatrogenic perforations of the oesophagus or trachea, can infect sternal wounds. The use of tight scrub-suits and laminar airflow are examples of means to reduce intraoperative wound contamination in the operating room. Plastic adhesive drapes on the skin are common practice but their use can be questioned, as their use has not been shown to reduce SSIs and might even increase recolonization of the skin and wound [31].

There is evidence that preoperative nasal screening for *S. aureus* and decolonization can reduce hospital-acquired wound infections caused by these bacteria. Furthermore, an approach of active surveillance of nasal MRSA, careful contact with carriers, proper hand hygiene, and awareness among staff can reduce transmission and infections with MRSA [32]. Postoperative contamination of wounds through haematogenous spread from intravenous and arterial catheters are best prevented by the use of coated catheters, proper hygiene routines among all staff and early removal of all catheters.

It is well documented that discriminative use of bone wax and electrocautery can lower the risk of infection. Additionally, meticulous surgical techniques, such as preservation of blood supply to tissues along with reduced surgical bleeding to avoid subsequent risk of reoperation and transfusions, are important. Sternal instability or dehiscence may be a consequence of a DSWI but can also promote bacterial growth and infection. It has been shown in cardiac surgery that a mechanically rigid fixation of the sternal halves reduces infection rate. There is increased risk of DSWI reported when less than seven sternal fixation wires are used with the authors proposing the standard use of nine or more wires [33]. Furthermore, several closing techniques with wires (single vs. figure-of-eight), plates, cables, or other newer devices have been reported, but larger prospective randomized trials are needed to verify if they are superior to conventional techniques. This does not apply to the lateral reinforcement technique named after Robicsek that was investigated in such a study and did not reduce the incidence of sternal wound complications in high risk patients [34]. Diabetes mellitus is a risk factor for SSI and suboptimal postoperative blood glucose control has been shown to increase the risk for SSI [7]. Therefore protocols for avoiding postoperative hyperglycaemia are important and generally implemented. Smoking is another well-defined risk factor for SSI and preoperative cessation of smoking can reduce postoperative complications, including SSIs [35].

Antibiotic prophylaxis reduces the SSI rate to approximately 1/5 compared to placebo and is recommended for all types of cardiac surgery. The first dose should be given immediately preoperatively as antibiotics need to be present in the tissues before contamination occurs. There is no additional effect of extending the prophylaxis to more than 48 h and a duration of 24 h may be sufficient and is practiced in many centers. To cover for both susceptible staphylococci as well as Gram-negative agents a second or third generation cephalosporin is often recommended [36], but the narrow-spectrum cloxacillin can also be used. Actually very low rates of Gram-negative SSIs have been reported with the use of cloxacillin, supporting that intraoperative contamination may be of little importance in Gram-negative wound infections [37, 38]. The use of glycopeptide antibiotics (vancomycin or teicoplanin) has been proposed in settings with high prevalence of MRSA, even though glycopeptides were inferior to beta-lactam antibiotics in a meta-analysis and are reported to increase the risk of acute kidney injury.

Local antibiotic prophylaxis with collagen-gentamicin has been evaluated since 2005 in several studies including four large randomized controlled trials (RCT), retrospective studies and in meta-analyses [39]. In brief, all RCTs but one [39], showed a reduction in SWI. Local application of vancomycin has been shown to be effective as well, although there are concerns regarding potentially high serum levels and the risk of selection of resistant strains to this important antibiotic. The use of antibacterial sutures with triclosan (2,4,4′-trichloro-2′-hydroxy-diphenylether), which is an antibacterial substance which reduces the growth of bacteria by inhibiting the fatty acid synthesis, has been shown in randomized studies to reduce the rate of leg wound infection [40] but not for sternal SSI [41, 42].

Conclusion

Sternal wound infection is a serious complication of median sternotomy in cardiac surgery, associated with significant mortality and morbidity. The pathogenesis of sternal wound infection involves a complex multifactorial process that includes a number of risk factors and pathogenic microorganisms. The management of this complication requires early and sufficient surgical debridement and appropriate antibiotic therapy.

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Atrioventricular Disruption

85

Sheena Garg and Shahzad G. Raja

High Yield Facts

- Atrioventricular disruption following mitral valve replacement (MVR) has a reported incidence of 0.5–2%.
- Atrioventricular disruption has a high mortality which varies between 50% and 93% with or without the use of cardiopulmonary bypass (CPB).
- Type I atrioventricular disruption is the most common type and located at the atrioventricular groove.
- The "early" rupture constitutes 2/3rd of the atrioventricular groove disruptions following MVR, and its resultant mortality may reach up to 50% despite immediate intervention.
- Both internal and external repair strategies are proposed to manage this catastrophic complication.
- Repair attempts without CPB risk propagation of injury and should not be pursued.
- All repair techniques are salvage procedures and the clinical circumstances dictate the choice of repair technique.

Introduction

Atrioventricular disruption following mitral valve replacement (MVR) is a rare but frequently lethal complication. It was first reported by Roberts and Morrow in 1967 [1]. The reported incidence is 0.5–2% [2–4]. However, as Karlson and colleagues [2] observe, the true incidence of this complication is likely underestimated, partly because sparse deaths tend not to be reported. Rapid exsanguinating hemorrhage results in high mortality which varies between 50% and 93% with or without the use of cardiopulmonary bypass (CPB) [5].

Types

Atrioventricular disruption after MVR have been classified into three types. In 1974, Treasure and colleagues [6] proposed 2 types according to the location of the epicardial tear and later on in 1977 Miller *and associates* [7] supplemented it with the type III rupture (Table 85.1). Sometimes, the ventricular tear progresses and becomes a mixed type, that is, combination of any of the three types. Depending on the time of tear following MVR, atrioventricular disruption has been further categorized as immediate, delayed, and chronic. "Immediate/early" tears occur in the operating room before or after weaning from CPB; hence, early resuscitation and better survival. "Delayed" tears present hours to days after leaving the operating theatre. Clinically, these present with massive bleeding into the drainage tubes and hypotension. "Chronic" tears occur days to years after MVR and present as left ventricular pseudoaneurysm [8, 9]. The "early" rupture constitutes 2/3rd of the atrioventricular groove disruptions following MVR, and its resultant mortality may reach up to 50% despite immediate intervention [10].

Table 85.1 Types of atrioventricular disruption

Type	Location	Description
I	Located at the A-V groove	The most common type Results from any injury of the MV annulus, such as excessive decalcification, insertion of an oversize prosthesis, deep sutures entering the myocardium and manual cardiac compression
II	Rupture of the LV posterior wall at the base of the papillary muscle	Primarily due to excessive resection of the posterior papillary muscle, with local hemorrhage and rupture
III	Rupture of the LV posterior wall between the base of the papillary muscle and the A-V groove	

A-V atrioventricular groove, *LV* left ventricle, *MV* mitral valve

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Pathogenesis and Risk Factors

Type I ruptures result from excessive debridement of a calcified annulus, endocarditis with an annular abscess, resection of the posterior leaflet, subannular placement of valve sutures, or elevation of the heart with an implanted prosthesis in place. Type II ruptures are consequent to excessive traction on, or resection of, the posterior papillary muscle. Type III ruptures occur after the placement of a high-profile stented tissue valve (especially in patients with a small left ventricle) with subsequent strut perforation of the ventricle, or from the aggressive use of rigid, hand-held suction devices [11].

Patient factors implicated in the pathogenesis are chronic rheumatic heart disease, excessive calcification of the MV apparatus, old age, female sex, myocardial ischemia, infective endocarditis with MV annular abscess, myocardial disease, hemodialysis and small left ventricular size (end-diastolic diameter <50 mm) [2, 8, 12].

Spontaneous type I tear has also been described after off-pump coronary artery bypass grafting [13]. In this case the mechanism of the reported spontaneous tear was likely related to the elevated left atrial pressure and over distention, tension on the atrioventricular groove while the heart was actively ejecting, and the use of an inotropic agent. Other contributing factors included cardiomegaly, previous myocardial infarction, advanced age, and the presence of diabetes mellitus [13].

The atrioventricular groove provides a naturally weakened transitional area [14]. Embryologically, the atrial and ventricular myocardium begin to separate in fetal life at approximately 7 weeks of gestation and complete separation is seen at 12 weeks [15]. Conduction tissue provides the only muscular continuity between the atria and ventricle in adult life. This vulnerable area provided the pressure release for the patient's overdistended, anatomically manipulated heart in off-pump coronary artery bypass grafting resulting in spontaneous disruption.

Significant distortion of the mitral annulus with enlargement of the left atrium and pulmonary veins has been demonstrated during manipulation of the heart for off-pump coronary artery bypass grafting [16]. George and colleagues [16] reconstructed the mitral valve structure at end diastole during manipulation for off-pump coronary artery bypass grafting using transesophageal echocardiography. They noted that the greatest distortion of the valve occurred during manipulation of the heart to view the lateral wall. Three-dimensional reconstruction of the mitral valve demonstrated that the intracardiac structures were folded primarily at the atrioventricular groove. The greatest mean percent increase in left atrial pressure (66%) was documented using a left atrial catheter in six patients during manipulation to perform the left circumflex coronary artery graft. The left atrial pressure increased by only 13% during performance of the left anterior descending artery graft and by 51% during the posterior descending artery graft construction. The increase in left atrial pressure was associated with an increase in left atrial dimension from 4 to 6 cm. The spontaneous atrioventricular groove tear after off-pump coronary artery bypass grafting reported is likely related to the heart manipulation that led to elevation in the left atrial pressure and size with resultant "pop-off" through the vulnerable atrioventricular groove.

Strategies to Minimize the Risk of Atrioventricular Disruption

Several intraoperative strategies can help to minimize the risk: (1) The posterior mitral leaflet in whole or part should be preserved in the high-risk patients, (2) the integrity of the MV annulus should be maintained by avoiding excessive debridement of the calcified annulus; this supports the MV on the left ventricular posterior wall, (3) judicious and limited papillary muscle excision is useful, (4) proper sizing of the MV prevents mechanical injury from an oversized prosthesis, (5) excessive traction on the ventricle should be avoided to prevent injury to the root of the papillary muscle, (6) complete adhesiolysis of adhesions from previous surgery helps in preventing excess traction on the left ventricle during surgery, (7) systemic hypertension after MVR should be prevented to reduce left ventricular workload, (8) in the high-risk patients, a pacemaker should be used to increase postoperative heart rate as it shortens diastole and avoids ventricular over-distension [8, 12, 17–20].

Management

Type I repairs necessitate removal of the prosthesis and internal repair that can incorporate a patch of residual posterior leaflet; a flap of atrial appendage, Teflon, or pericardium (Fig. 85.1) [21]; atrialization of the rupture; or autotransplantation [11]. A pocket patch of pericardium sutured in place from the ventricle to the atriotomy has also been described. Having been left open at the top, the space between the ventricular wall and the patch is filled with BioGlue® Surgical Adhesive-impregnated Teflon (CryoLife Inc.; Kennesaw, GA). The prosthesis is then reimplanted, with the top of the pocket patch incorporated into the atriotomy closure [22]. External repair can be used in type II and type III repairs [3, 5, 9, 11].

The concept of internal repair is elegant. However, it represents a major undertaking that requires the patient to possess considerable physiologic reserve. CPB must be reinstituted, the prosthesis explanted, the mitral annulus reconstructed using a patch, and a prosthesis reimplanted.

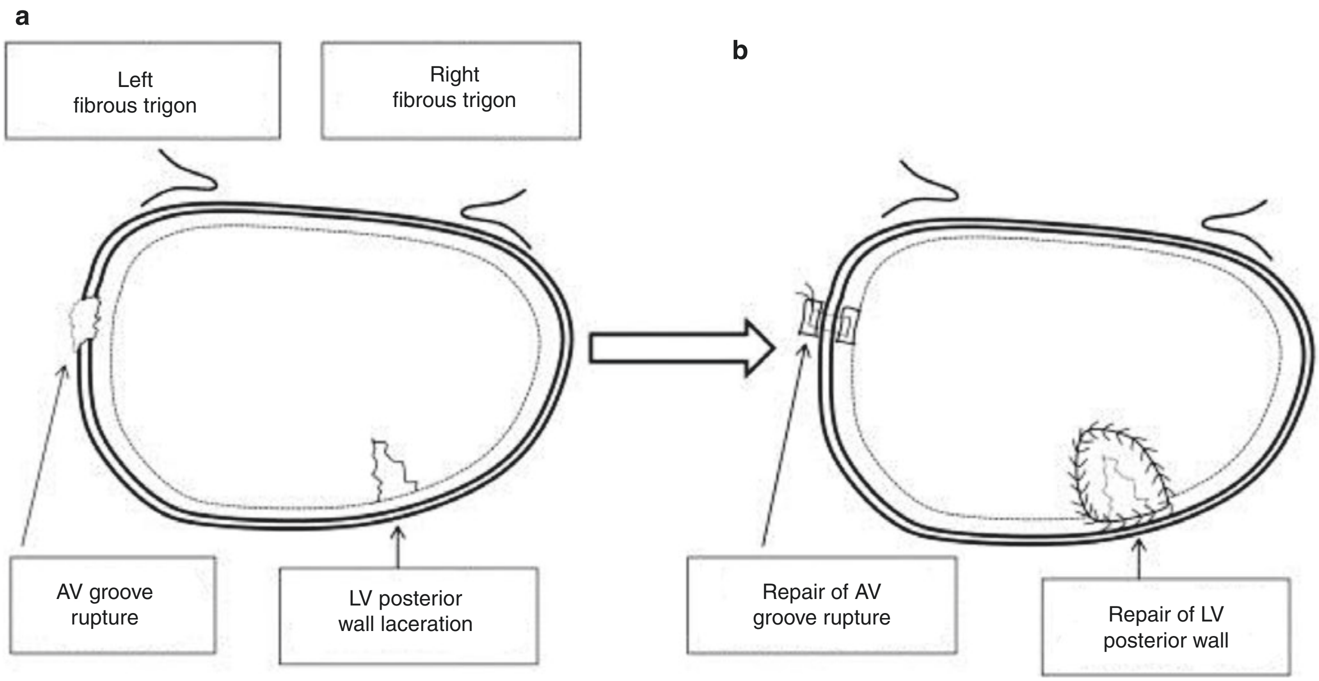
a
Left fibrous trigon
Right fibrous trigon
AV groove rupture
LV posterior wall laceration
b
Repair of AV groove rupture
Repair of LV posterior wall

Fig. 85.1 Internal repair of atrioventricular groove disruption after mitral valve replacement. (**a**) The small tear of atrioventricular groove and laceration of posterior left ventricular wall. (**b**) A simple bovine pericardial pledgetted suture was placed at the small tear site of atrioventricular groove and bovine pericardial patch was sutured to the healthy endocardium of the left ventricular posterior wall. (Reproduced from Copyright © 2014 Kwon et al. [21]; licensee BioMed Central Ltd.)

Given a patient able to tolerate a prolonged additional operation, the internal technique likely offers the most durable reconstruction. Reality is quite different, however, as evidenced by the high mortality rates of this approach [23].

The external repair could be construed as less precise but may offer the dying patient a higher likelihood of salvage. The "best" anatomic repair is of no benefit to a patient who does not survive [23].

Currently the best repair strategy, "internal" vs. "external," remains undefined and general consensus is that clinical circumstance must dictate operative strategy.

Complete cardiac decompression is critical for safe repair. Repair attempts without CPB risk propagation of injury and should not be pursued. All attempted repair procedures, either internal or external, should be performed on full CPB with cardioplegic cardiac arrest. When CPB was used during repair of LV rupture, reported survival rates were 67% after external repair and 27% after internal repair; without CPB, the survival rates decreased to 50% and 7%, respectively [2].

The benefits of ensuring cardiac decompression in the immediate postoperative period are less clear but conceptually sound [23]. Various adjunct measures have been advocated in the literature to optimize conditions for healing [24]. Medical afterload reduction, blood pressure control and intra-aortic balloon counterpulsation use for hemodynamic instability are all strategies that contribute to cardiac decompression. Extracorporeal membrane oxygenator support postoperatively as a mechanical means of decompressing an injured, edematous heart has also been reported [23].

Conclusion

MVR can be complicated by rupture or dehiscence of the posterior atrioventricular groove. Atrioventricular disruption is a difficult and major complication of MVR. This condition occurs rarely but is usually fatal with a very high operative mortality rate. A variety of internal and external repair techniques have been reported to treat this catastrophic complication. All these techniques are salvage procedures and the clinical circumstances dictate the choice of repair technique.

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Part VII

Paediatric and Congenital Heart Disease

86

Pediatric Cardiopulmonary Bypass and Hypothermic Circulatory Arrest

Craig M. McRobb, Scott Lawson,
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High Yield Facts

- Pediatric cardiopulmonary bypass (CPB) is necessary to operate inside the heart and on portions of the aorta.
- Key CPB components include an oxygenator and a blood pump.
- CPB provides oxygenated blood flow while the heart is arrested, and ventilation is stopped.
- CPB has become safer, simpler, and with lower morbidity.
- Pump flow is the main determinant of oxygen delivery on CPB.
- Deep hypothermic circulatory arrest (DHCA) involves deep cooling of the patient and cessation of blood circulation.
- DHCA allows repair of very complex intracardiac defects and defects involving the transverse aortic arch.
- Antegrade cerebral perfusion decreases or eliminates cerebral circulatory arrest.

Introduction

Modern cardiopulmonary bypass (CPB) originated from the work of Gibbon who described the first artificial oxygenation device, which he termed the heart lung machine [1]. Gibbon performed the first successful use of the heart lung machine to repair an atrial septal defect in a child on May 6, 1953. Thereafter, the use of the heart lung machine and CPB was expanded to deal with more complex congenital heart defects and eventually to the repair of acquired adult cardiac lesions. Since the early era of pediatric CPB there have been major advances in heart lung machine technology, CPB equipment and techniques, and surgical interventions [2, 3] allowing for safe repair of even the most complex heart defects.

CPB is the technique of diverting venous blood as it nears or enters the heart to an extracorporeal (outside the body) circuit (ECC) and then pumping this blood (now artificially oxygenated) back into the aorta—bypassing the heart and lungs. Since the blood is being pumped by an artificial pump, the heart is often arrested (see Chap. 10). Since the venous blood is no longer flowing through the lungs, ventilation of the lungs may be stopped. This combination allows a cardiac surgeon to operate on, or inside, a heart that is blood free, in a motionless surgical field, on a fully supported patient. This allows precise surgical correction of complex acquired or congenital cardiothoracic defects.

CPB is necessary for many pediatric operations described in the following chapters. The ECC contains key disposable components including a venous reservoir, blood pump, heat exchanger, oxygenator, and arterial filter. This is attached to the heart lung machine which contains blood pumps, pressure/temperature monitoring, safety devices, blood gas analyzers, gas blenders, timers, vacuum regulators, and control/monitoring panels (Fig. 86.1a, b). The heart lung machine is operated by medical professionals known as perfusionists. Other ancillary equipment includes heater coolers, cell saver/autotransfusion devices and blood analyzers.

Conduct of Cardiopulmonary Bypass

Anticoagulation

The first step towards placing a patient on CPB is to anticoagulate the patient. This is necessary due to the large foreign

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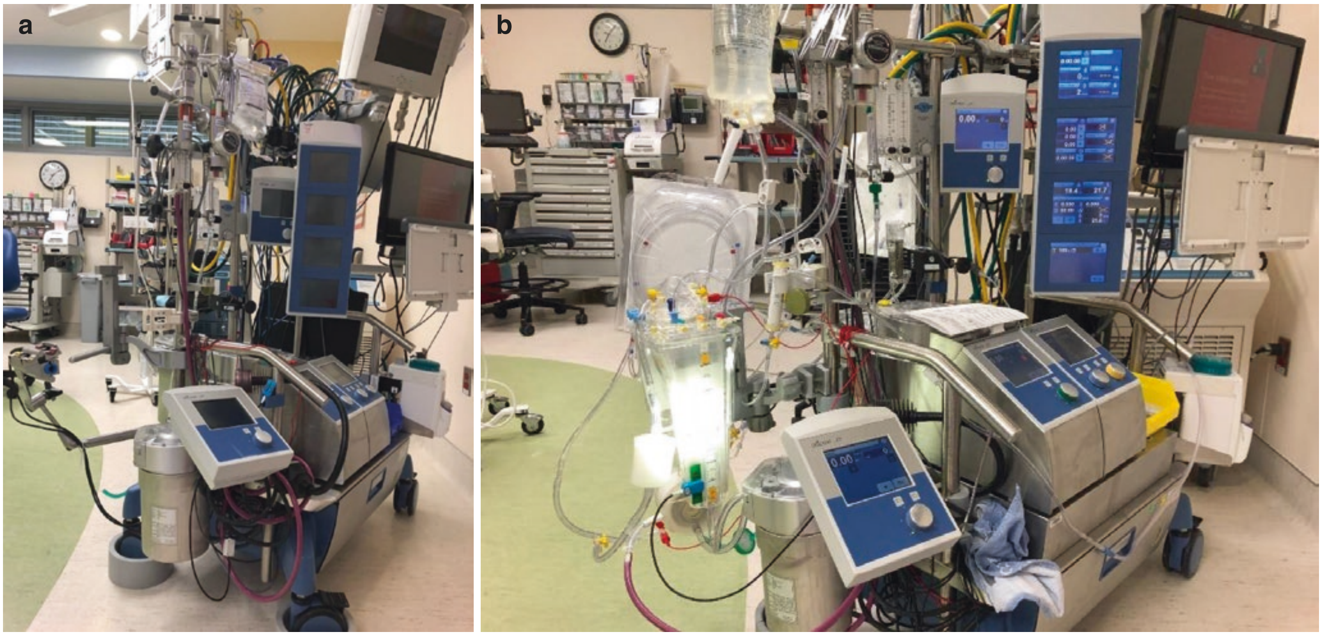

Fig. 86.1 (**a**) Heart lung machine. (**b**) Heart lung machine with disposable cardiopulmonary bypass circuit attached

surface that the blood will be exposed to in the ECC. Heparin is the most commonly used anticoagulant due to the ease of measuring its effectiveness via a test known as the activated clotting time (ACT), and the fact that it has a reversal agent (protamine). Heparin works by binding with antithrombin III (ATIII) and potentiating ATIII's effects on thrombin and factor Xa. Heparin dosing regimens vary but range from 300 to 500 units/kg with a target ACT to commence CPB of >480s. Other anticoagulants, such as the direct thrombin inhibitor bivalirudin, may be used in the case of patients with heparin-induced-thrombocytopenia (see Chap. 12). Once the ACT is adequate, pump suckers from the heart lung machine may be turned on. This suction allows shed blood during cannulation, and CPB, to be pumped from the surgical field into the venous reservoir of the ECC where it remains in the circulation.

Arterial Cannulation

Once heparin is administered cannulation is performed. Cannulas are large catheters that are inserted into the patient and serve as the interface between the patient's vasculature and the ECC. For pediatric CPB many sizes and shapes of cannula are necessary (Fig. 86.2a, b). Arterial cannulation is usually done first. The typical location is the ascending aorta but depending on the operation and patient anatomy, different, or additional locations may be cannulated. The size and location of the arterial cannula is very important as this is where oxygenated blood from the ECC will be pumped into the patient. An arterial cannula that is too small may not allow for adequate pump flow to meet the patient's metabolic demands and may result in damage to the red blood cells and the patient's vasculature. The arterial cannula is attached to tubing that comes from the outlet of the ECC oxygenator. A common practice is to perform a "test infusion" from the heart lung machine to the patient. This confirms successful placement of the arterial cannula tip in the lumen of the cannulated vessel. Aortic dissection is a possibility from aortic cannulation and must be quickly diagnosed. After a successful test infusion, volume from the venous reservoir can be pumped into the patient. This is often necessary due to blood loss from aortic and venous cannulation and helps maintain patient stability just prior to CPB initiation.

Venous Cannulation

A single venous cannula (single-stage or 2-stage) or multiple cannulas (bi-caval) are inserted to allow drainage of venous blood to the ECC. The method of venous cannulation used depends on the operation and individual surgeon's discretion. Appropriately sized venous cannulae are important, to assure proper venous drainage and avoiding venous congestion in the patient.

Femoral Cannulation

Many pediatric cardiac operations involve redo median sternotomies. In this case, it may be necessary to proactively

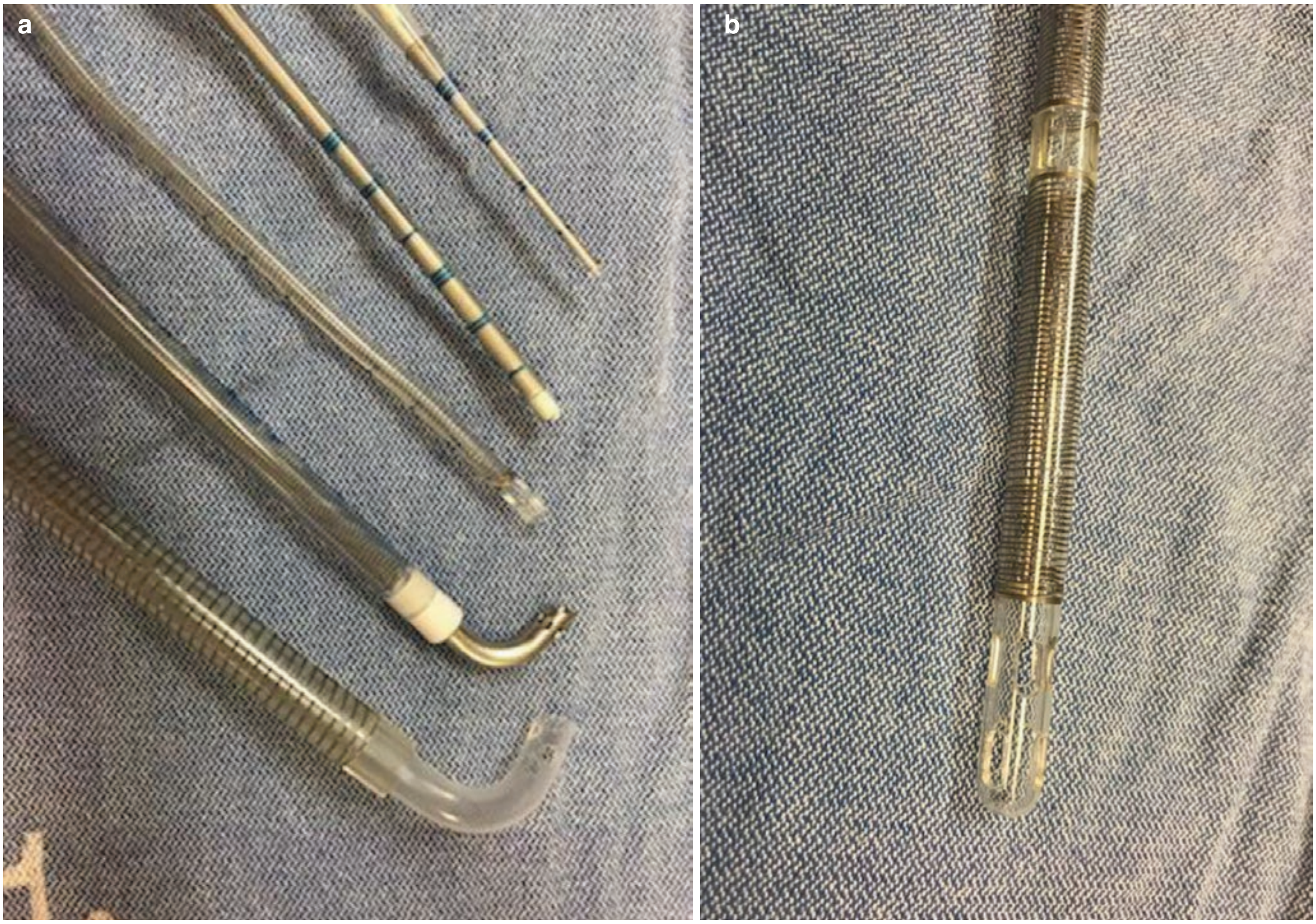

Fig. 86.2 (**a**) Different types of pediatric venous and arterial cannulae. (**b**) Bi-caval venous cannula: for larger pediatric patients/adults; gets inserted through the right atrium with the tip placed in the inferior vena cava. Upper holes drain the right atrium

cannulate the femoral artery and femoral vein (fem-fem) and initiate CPB. This allows decompression of the heart prior to risky redo sternotomies. In the case of massive hemorrhage during redo sternotomy a plan should be in place to rapidly initiate fem-fem CPB, or otherwise stabilize the patient until direct cannulation can occur.

Initiation of Cardiopulmonary Bypass

Once the arterial and venous cannulas are attached to the ECC, and the patient is adequately heparinized, the patient may be placed "on bypass". Clamps are removed from the venous and arterial lines of the ECC and drainage of venous blood to the venous reservoir is achieved either by gravity (siphoning of blood due to the height difference from the right atrium to the venous reservoir) or via vacuum assisted venous drainage (VAVD). VAVD, commonly used for pediatric CPB, is achieved by applying negative pressure to the venous reservoir. This allows the venous reservoir and oxygenator to be raised to a level nearer the patient and for adequate venous drainage with shorter tubing length, smaller diameter tubing and smaller venous cannulas. This reduces the prime volume and foreign surface of the ECC, potentially reducing transfusion requirements.

As the venous blood is being drained from the patient, the arterial pump flow is increased to a flow that is roughly equivalent to the output of the native heart. Once on "full flow" the heart should no longer be ejecting, the central venous pressure should be zero, volume that was in the heart and pulmonary vasculature is now in the venous reservoir of the CPB circuit (Fig. 86.3), and the arterial pressure tracing should be relatively flat. Unlike the pulsatile pumping of the heart the mechanical pumps commonly used for CPB are continuous flow pumps (like a garden hose). For pediatric CPB an arterial roller-pump is most common. This style pump offers finer control of pump flow at lower flows (particularly important for procedures like antegrade cerebral perfusion in neonates). While still considered continuous flow pumps they do actually generate a pulse pressure which

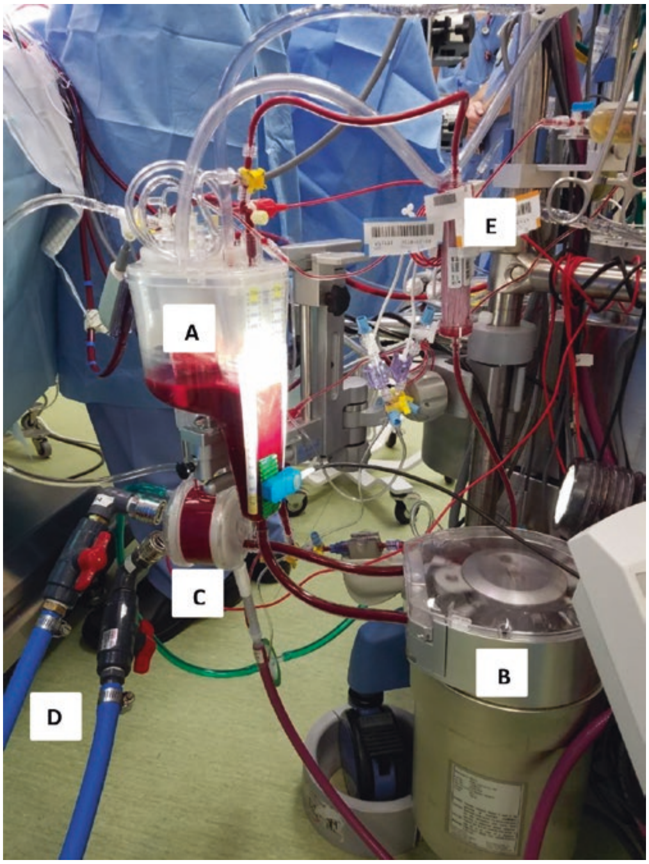

Fig. 86.3 Venous reservoir (**a**); arterial roller pump (**b**); oxygenator with integrated arterial filter (**c**); water lines attached to the heat exchanger portion of the oxygenator (**d**); ultrafiltration device (**e**)

may be confused with cardiac ejection when evaluating the arterial pressure tracing (Fig. 86.4a–c). Centrifugal pumps are true continuous flow pumps which are more frequently used for adult CPB, larger paediatric patients, and ECMO.

Blood Flow Through the Cardiopulmonary Bypass Circuit

The CPB pump pulls venous blood out of the venous reservoir and pumps it into the heat exchanger portion of the oxygenator at a rate that is controlled by the perfusionist. The heat exchanger is often integrated into the oxygenator and is most commonly made of stainless steel. Blood flows on one side of the stainless steel with water being pumped through the other side by a separate heater-cooler device. The temperature of the water is adjusted which indirectly affects the temperature of the blood. This provides precise control of patient temperature allowing the patient to be cooled to as low as 18 °C and then rewarmed to normal body temperature.

After the heat exchanger blood flows through the gas exchange portion of the oxygenator. This is commonly made up of micro-porous hollow-fibers with blood flowing on the outside of the fibers and gas (mixture of room air and oxygen) flowing through the inside of the fibers. Gas molecules such as O_2 and CO_2 are small enough to travel through the micropores of the hollow-fibers (blood cells are much too large). Just like in the lungs, O_2 and CO_2 flow from high concentration to low concentration (Fick's Law). In an oxygenator, this means O_2 flows from the gas side to the blood side (eventually binding with hemoglobin to make oxyhemoglobin), and CO_2 is transferred from the blood side into the gas side, where it exits the oxygenator through an exhaust port. Inhalation anesthetic agents are also commonly added to the oxygenator gas flow to maintain anesthesia while the ventilator is off.

The perfusionist evaluates and controls blood oxygenation and CO_2 removal. This is accomplished via continuous arterial blood gas monitoring, blood gas analysis, and adjusting the FiO_2 and the rate of continuous gas flow (sweep rate) through the oxygenator. Increasing the FiO_2 of the ventilating gas results in an increase in the patient PaO_2. The oxygenator sweep rate is similar to adjusting the rate on a ventilator—sweep rate and patient $PaCO_2$ have an inverse relationship. For pediatric CPB it is often necessary to add CO_2 to the ventilating gas of the oxygenator due to the relatively large surface area for gas exchange, efficiency of modern oxygenators at removing CO_2, and the use of hypothermia (decreased patient CO_2 production).

As blood exits the oxygenator it goes through an arterial line filter (ALF) (either a stand-alone device or often integrated into the oxygenator). The ALF is an important safety device that protects the patient from emboli (gaseous or particulate) from the ECC. From the ALF the blood travels up the arterial line to the arterial cannula and into the patient.

Pump Flow/Oxygen Delivery

Pump flow is the main determinant of O_2 delivery (DO_2) during CPB (DO_2 = indexed pump flow × 10 × arterial O_2 content). Anticipated full flow for a patient is mainly determined by calculations based on body weight in kilograms (Table 86.1). Pump flow is adjusted up or down based on the clinical scenario. The metabolic demands of the patient must be balanced with the surgeon's need for a bloodless surgical field. Pump flow should deliver oxygenated blood at a rate that meets the metabolic demands of the entire body (brain, kidney, gut, heart, etc.), as determined by SVO_2, near-infrared spectroscopy (NIRS), pH, electrocardiogram, lactate, etc. This flow should generate a mean arterial pressure (MAP) that provides adequate perfusion pressure for all major organs. Patient's systemic vascular resistance and

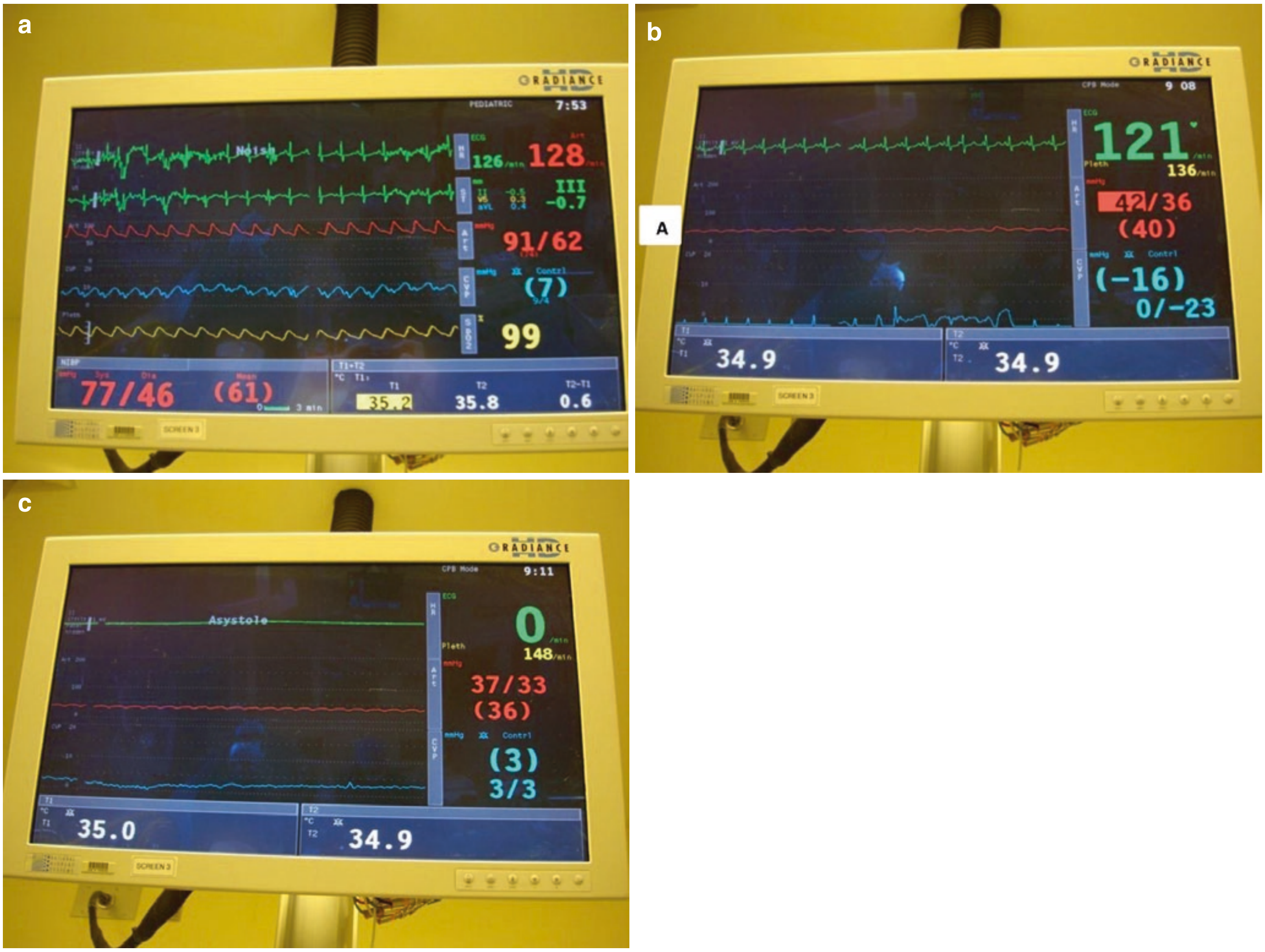

Fig. 86.4 (**a**) Pre-cardiopulmonary bypass patient hemodynamics. (**b**) On-cardiopulmonary bypass patient hemodynamics with flat arterial tracing (**a**). Minor pulsatility from arterial roller pump can be seen. Heart is beating but empty. CVP is <0. (**c**) On-cardiopulmonary bypass patient hemodynamics with aortic cross clamp on. Asystole on electrocardiogram

Table 86.1 Recommended cardiopulmonary bypass flow rates for different sized patients

Patient weight (kg)	CPB flow rate (ml/kg/min)
2–7	120–200
7–10	100–175
10–20	80–150
➢ 20	50–75

CPB cardiopulmonary bypass

pump flow may need to be adjusted (up or down) to maintain an adequate MAP during CPB. Other factors that determine MAP include blood temperature and hematocrit (via blood viscosity).

At this point, depending on the operation, it is possible to arrest the heart and perform an operation inside the motionless, bloodless heart in a very stable patient. This allows the repair to be conducted by a surgeon in an ideal, non-hurried condition.

Goal-Directed-Perfusion

There has been a recent trend towards goal-directed-perfusion (GDP). This involves more extensive monitoring and maintaining certain parameters (DO_2, MAP, SVO_2, NIRS, etc.) within pre-determined ranges during CPB (or reducing the amount of time below these ranges), as well as the usage of newer oxygen consumption/CO_2 production based ratios to guide pump flow/DO_2. This would be an improvement to weight based flow estimates (Table 86.1). The goal is to develop individual-patient based perfusion strategies, with known critical values to avoid, with the intention of avoiding some known consequence (i.e. acute kidney injury [AKI]). Rannucci et al. and others have focused on nadir DO_2 on CPB and a correlation with post-CPB AKI in adults, as well as the ratio of O_2 delivery to CO_2 production (DO_2/VCO_2), with a ratio <5 being predictive of hyperlactatemia and AKI [4–6].

While some research has focused on pediatric GDP [7–9], most studies involve adult CPB. The development of pediatric GDP guidelines will be difficult, due to the non-homogenous patient population. Multiple strategies would have to be studied and developed for populations like: neonates, single ventricle patients, cyanotic vs. non-cyanotic patients, etc.

A problem historically with assessing DO_2 adequacy during CPB is it's based on global markers of perfusion (pH, SVO_2, lactate). Good oxygenation/perfusion in many areas can mask an area(s) with poor perfusion, undergoing anaerobic metabolism. An adjunct to pediatric GDP could be incorporating more organ specific monitoring techniques, such as renal and splanchnic NIRS.

Vents/Pump Suckers

CPB vents are suction catheters, often placed inside or around the heart, or in the aorta. The catheter is attached to tubing which runs through a roller pump, which pumps the blood into the venous reservoir of the ECC. This keeps any blood aspirated by the vent in the patient's circulation (as opposed to lost to a waste suction cannister). Intra-cardiac vents help with surgical visualization and with de-airing the heart prior to cross-clamp removal.

Pump suckers are hand-held suction that are also attached to the reservoir via a pump and tubing. The usage of pump suckers while the patient is heparinized, and cell saver suction prior to heparinization and after heparin reversal, are commonly used in both adult and pediatric CPB to prevent blood loss from the patient.

Once protamine is given, vents and pump suckers can lead to protamine getting into the ECC and clotting the circuit. This makes it unusable if the patient needed to go back on CPB. It is important to be sure vents and pump suckers are off once protamine is started.

Weaning from CPB

Once the operation is completed, weaning from CPB may occur. At this point, the heart should be beating (but empty); the ventilator should be on with appropriate settings; inotropic support and pacing should be started (if necessary); and patient's temperature and blood values (hematocrit, electrolytes, pH etc.) should be optimized. To smoothly transition a patient off CPB, the pump flow is gradually decreased as the cardiac output gradually increases to full cardiac output. This is accomplished by gradually clamping the venous line, filling the heart with blood from the venous reservoir, and reducing pump flow. Once hemodynamics are adequate, and pump flow is minimal, the patient can be taken "off bypass". The venous line is clamped and the arterial pump is stopped. Residual blood volume from the ECC circuit may continue to be transfused into the patient to keep up with bleeding and to salvage blood remaining in the circuit into the patient. The venous cannula is removed and protamine can be given to reverse the heparin. Eventually the arterial cannula is removed and the patient is no longer attached to the heart lung machine. The ECC remains primed until the chest is closed in case re-initiation of CPB becomes necessary.

Deep Hypothermic Circulatory Arrest

Deep hypothermic circulatory arrest (DHCA) is a CPB technique where patients are deeply cooled and the pump flow is stopped. Cerebral metabolism decreases by 6–7% for every 1 °C decrease in temperature below 37 °C. Different organs' metabolisms are affected at different rates. The purpose of DHCA is to decrease metabolic demand so that CPB can be interrupted for 30–60 min to facilitate surgical repair. Patients are typically cooled until they reach a core temperature of 18–20 °C, the CPB pump is turned off, and the patient is exsanguinated into the CPB reservoir (Fig. 86.5a, b). For intracardiac repairs, DHCA allows for a bloodless surgical field where collateral return may be high. During arch reconstruction DHCA allows the surgeon to work on the entire transverse arch without the high-pressure arterial flow from the aortic cannula. Rimmer et al. describe the history and development of DHCA [10].

DHCA is commonly used during congenital cardiac repairs for both neuro-protection and to facilitate many surgical approaches. For paediatric cardiac surgery, which now often involves minimally invasive techniques such as partial sternotomies and mini-incisions, cannulas used for CPB can be obtrusive and make visualization extra challenging. DHCA allows removal of venous and arterial cannulas to aid in surgical visualization.

Improvements in surgical techniques have decreased the use of DHCA for routine cases. DHCA is still commonly employed during complex aortic arch repair, specifically repairs involving the transverse aortic arch. Techniques including selective cerebral perfusion (SCP) have caused a decrease in the use of DHCA, and have allowed for a lesser degree of hypothermia during aortic repairs. Increasingly more congenital repairs are being done using normothermia or mild hypothermia without an increase in sequelae. Today many operations only involve periods of lower-body circulatory arrest with the brain being continuously perfused.

Important considerations for DHCA include: target core temperature; degree of hemodilution; cooling and rewarming rates; use of intermittent re-perfusion; blood gas strategy (alpha-stat vs. pH-stat); and hyperoxia. An advantage of using a pH-stat blood gas strategy during cooling is it prevents the

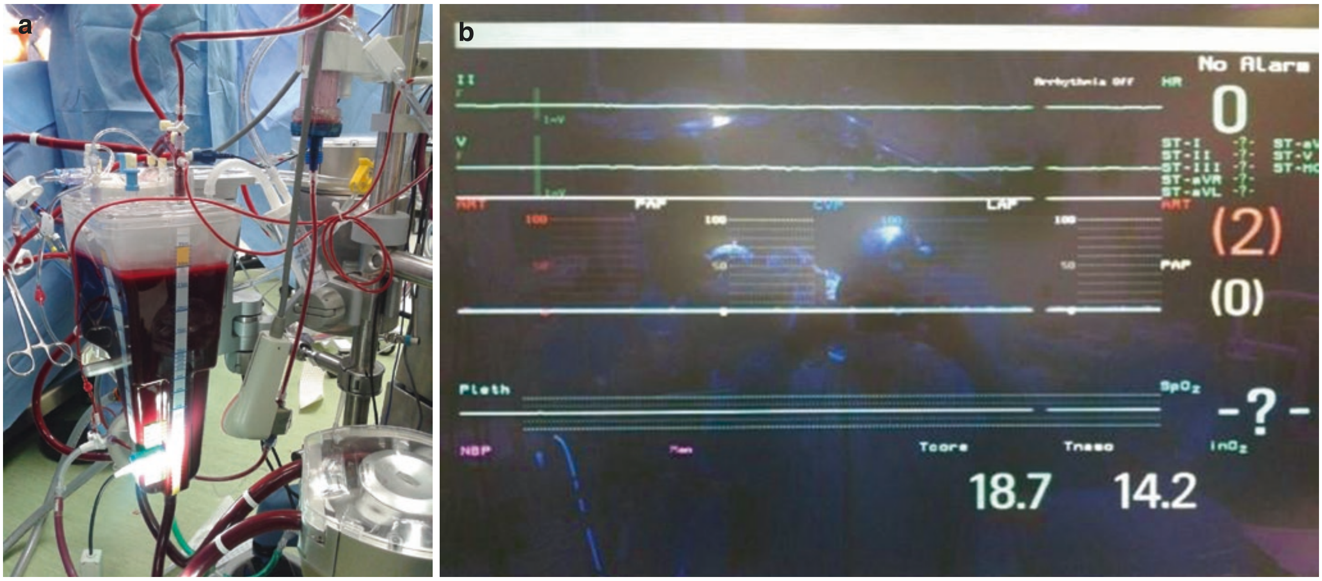

Fig. 86.5 (**a**) Venous reservoir full of blood during deep hypothermic circulatory arrest. (**b**). Hemodynamic monitor during deep hypothermic circulatory arrest. Mean arterial pressure is near zero. Core patient temperature = 18.7 °C

profound cerebral vasoconstriction that can occur at low arterial blood temperatures. This allows uniform cooling of the brain prior to circulatory arrest. The usage of cerebral monitoring is an important adjunct to DHCA.

Adult Versus Pediatric Cardiopulmonary Bypass

Pediatric and adult CPB have many similarities and differences. Differences can be described as they relate to CPB circuitry (and patient's physiologic interaction with the circuit); CPB management; and patient anatomy and physiology.

The main circuit components, configuration, and flow through a pediatric CPB circuit are similar to adult CPB. However, since the size range of patients for paediatric CPB varies from less than 2 kg to >100 kg, multiple size oxygenators and different size tubing and other components are often necessary.

CPB circuits are constructed of artificial polymers which activate many inherent biological systems designed to protect the body from foreign invaders [11]. Blood component exposure to foreign materials results in a systemic inflammatory response [12], and the severity of this response is directly correlated to the amount of foreign surface area and the length of time on CPB [13]. Current CPB circuits can be equal to or exceed the surface area of a neonate's body surface area. In contrast, an adult CPB circuit may be only 1/5th of an adult's body surface area. Therefore, pediatric patients are at higher risk of CPB sequelae.

In addition to the activation of inflammatory mediators, the coagulation system is commonly deranged due to a range of hemostatic defects resulting from cardiac surgery and CPB [14] (as well as immature hepatic function in neonates). This can be a result of the circuit's prime volume, contents, and shear stresses encountered as blood is exposed to the foreign surfaces and non-physiological pressures and pathways.

Unlike adult CPB, it is common in pediatric CPB to utilize a blood prime to avoid extreme hemodilution. Also, because of the lower blood volume in pediatric patients, small changes or shifts in blood volume that can occur during an operation, including bleeding into drapes, aspiration into a waste suction or cell saver, filling of vent tubing, or priming the cardioplegia circuit can have a significant impact on the venous reservoir level and the overall volume status of the patient/ECC circuit. By contrast, decreases of 100 ml or greater in the adult CPB venous reservoir is often insignificant.

Another key difference between adult and pediatric CPB is the impact of shunts. The three types of shunts are: circuit, anatomic, and surgically created. Shunts in the ECC divert blood through different components of the ECC and back to the reservoir (not to the patient). For pediatric CPB this shunting of flow away from the patient can be a significant portion of pump flow, often requiring a flow probe to measure actual blood flow to the patient to assure adequate perfusion. Circuit shunt flow in adult CPB is an insignificant portion of overall pump flow to the patient.

Anatomic and surgical shunts (aorto-pulmonary) are frequently encountered in the congenital heart disease population. It is vital that these are considered when planning for pediatric CPB. These shunts can affect the surgeon's surgical field; overall perfusion of the patient; cannulation strategy; myocardial protection; vascular line placement; sternotomy/entry strategy; and cooling and rewarming of the patient.

Pediatric patients require much higher flow rates than adults to meet metabolic demands. Neonates are often perfused at flow rates up to 200 ml/kg/min whereas adult flow rates may approximate 50 ml/kg/min. Thermoregulation in small children is also impaired necessitating close attention to temperature monitoring.

See Chap. 87 for differences between the adult and pediatric myocardium and cardioplegia strategies.

Modified Ultrafiltration

Modified ultrafiltration (MUF) is a technique that is used more commonly with pediatric CPB. The technique is performed immediately after weaning from CPB. MUF involves removal of ultrafiltrate from the patient while adding an equal volume of residual CPB circuit blood [15]. The purpose is to salvage residual CPB blood into the patient, remove extravascular water (edema), remove inflammatory mediators, increase hematocrit and concentrate coagulation factors. MUF originated in an era of very high ECC prime volumes and severe patient hemodilution. MUF's utilization varies in different parts of the world [16]. Today, patients have much less extravascular water, experience less hemodilution, less residual CPB volume, less inflammation, and often can be weaned with a higher hematocrit when not performing MUF. A disadvantage of MUF is that it adds to the complexity and prime volume of the CPB circuit as well as the complexity of the immediate post-CPB period. MUF can take up to 20 min and extends the patient exposure time to the CPB circuit. Some centers report no longer performing MUF or not performing MUF in smaller patients [17–19].

Conclusion

Historically pediatric CPB was a very risky undertaking. With advances in CPB techniques, circuitry and surgical techniques nearly all congenital heart defects may now be successfully repaired. Today even complex repairs are completed with very low morbidity and mortality rates. Future improvements should aim to make CPB even more biocompatible and further reduce the inflammatory response to CPB.

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Myocardial Protection in Children

87

Abdullah Doğan and Rıza Türköz

High Yield Facts

- Similar myocardial protection methods have been used in adult and pediatric groups for several years. However, the immature heart in a pediatric patient differs in many ways from the mature heart in an adult patient.
- The two contemporary myocardial protection methods used in pediatric cardiac surgery are cardioplegic arrest (for intracardiac operations) and on-pump beating heart (for extracardiac and isolated right-side operations).
- In clinical use, cardioplegia is generally classified either as crystalloid (intracellular and extracellular solutions) or blood cardioplegia.
- Commonly used, extracellular cardioplegic solutions are St. Thomas no. 2, Buckberg, del Nido, and the intracellular solution is histidine-tryptophan-ketoglutarate.
- The del Nido solution does not require frequently repeated administration. Hence, it is widely used.
- Many factors can lead to post-operative low cardiac output syndrome such as acidosis, electrolyte imbalance, and residual cardiac defects.
- If the morbidity and mortality rate is high, particularly in long and complex procedures, revision of the myocardial protection method must be taken into account.

History of Cardioplegia

The first cardioplegic arrest was used by Melrose [1] in 1955. In the following 20 years, the mortality rate in cardiac surgery remained between 10% and 20% [2]. During this period, the myocardial protection methods included systemic and/or topical hypothermia [3–8], continuous or intermittent aortic occlusion [9], aortic root or intracoronary blood perfusion [10, 11], or electrically induced ventricular fibrillation [12]. The first successful pharmacological arrest was used by Bretschneider in 1964, and this was the initial form of today's histidine-tryptophan-ketoglutarate (HTK) solution [13].

Application of myocardial protection methods is important during cardiac surgery to prevent irreversible ischemic damage that otherwise starts to occur in the normothermic human heart only 20 min after the ischemia [14]. Current techniques are able to extend this duration up to 4–5 h without causing any myocardial damage in cardiac transplantation [15].

Differences Between Pediatric and Adult Hearts

Similar myocardial protection methods have been used in adult and pediatric groups for several years. However, the immature heart in the pediatric group differs in many ways from the mature heart in adults. These differences are listed below.

1. Morphologically, in the newborn heart, only 30% of the myocardial mass comprises contractile tissue compared with 60% in the mature myocardium [16].
2. Pediatric myocardium has fewer mitochondria and less oxidative capacity [16].
3. In the adult myocardium, up to 90% of adenosine triphosphate (ATP) production is derived from the oxidation of fatty acids [17]. In contrast, the main substrate for the neonatal heart is glucose [18].
4. Experimentally, normal immature myocardium has a greater tolerance to ischemia when compared to mature myocardium [19], because immature myocardium has greater glycogen stores and more prolonged anaerobic utilization of glucose than in the adult heart [20, 21]. During ischemia in the newborn heart, ATP depletion is

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delayed due to diminished activity of 5′-nucleotidase which catalyzes the reaction of adenosine monophosphate to adenosine [21].

5. Physiologically, immature myocardium has decreased ventricular compliance, less preload reserve, decreased sensitivity to catecholamines, less inotropic reserve (with maximum adrenergic stimuli), and more negative inotropic response to anesthetic agents [22, 23].
6. The immature myocardium is more sensitive to extracellular calcium than mature myocardium [24, 25]. The sarcoplasmic reticulum is underdeveloped in the pediatric heart, has reduced storage capacity for calcium, and the activity of the sarcoplasmic calcium ATPase is lower than that of the adult heart [26].
7. Cardiac output in pediatric patients is more dependent on heart rate and sinus rhythm. The increase in afterload produces significant hemodynamic impairment.

Methods of Myocardial Protection

The two contemporary myocardial protection methods used in pediatric cardiac surgery are cardioplegic arrest and on-pump beating heart. Cardioplegic arrest is used in most of the intracardiac operations. On-pump beating heart technique can be used in extracardiac and isolated right-side operations, including bidirectional cava-pulmonary anastomosis, extracardiac Fontan, tricuspid, or pulmonary valve surgery.

The essential principle of cardioplegia is to achieve rapid cardiac arrest. For the chemical arrest, mainly K^+ is used. In addition, magnesium, calcium antagonists, local anesthetic agents (lidocaine, procaine) are also used [27]. The advantages of cardioplegia are the diastolic arrest of the contractive components, cessation of electrical activity, reduction of metabolic activity, intermittent oxygen delivery (especially with blood cardioplegia), maintaining acid-base balance, maintaining high osmotic pressure, modifying reperfusion, reversibility, and low toxicity.

In clinical use, cardioplegia is generally classified into two groups: crystalloid and blood cardioplegia. Crystalloid cardioplegia is further split into the following two subgroups: intracellular and extracellular solutions. Examples of extracellular cardioplegic solutions, currently used, include St. Thomas no. 2 (Table 87.1), Buckberg and del Nido. A typical example of the intracellular cardioplegic solution is Histidine-tryptophan-ketoglutarate (HTK) solution (also known as Custodiol) (Table 87.2).

Table 87.1 Components of St. Thomas no. 2 solution (Plegisol)

Component	Concentration (mmol/L)
K^+	16
Na^+	110
Ca^{2+}	1.2
Mg^{2+}	16
Cl^-	128
$NaHCO_3$ 8.4%	10

Table 87.2 Components of HTK solution (Custodiol)

Component	Concentration (mmol/L)
K^+	9
Na^+	15
Mg^{2+}	4
Ca^{2+}	0.015
Ketoglutarate	1
Tryptophan	2
Histidine	198
Mannitol	30

HTK histidine-tryptophan-ketoglutarate

Intracellular-type cardioplegia contains low concentrations of Na^+ and Ca^{2+}, while extracellular-type contains high concentrations of Na^+, Ca^{2+} and Mg^{2+}. Cardioplegia solutions with magnesium and low calcium content, containing glucose and buffering solutions have been commonly used in most of the cardiac centers [28]. Many other substrates including insulin, adenosine, oxygen-derived free radical scavengers, procainamide, beta-blockers (esmolol), Na^+, H^{2+} exchange inhibitor (amiloride, cariporide), Na^+ blockers (lidocaine, tetrodotoxin), L-Arginine, K^+ channel openers (aprikalim, pinacidil, nicorandil), and Ca^{2+} channel blockers have been used in experimental studies [2]. However, most of them are not used in clinical practice [2].

Crystalloid and blood cardioplegia are both widely used in clinical practice. Crystalloid cardioplegia has some advantages: It is inexpensive, easy to deliver, and one single application is sufficient [29, 30]. It has been demonstrated that a single dose of HTK is adequate for myocardial protection up to more than 2 h of ischemia in pediatric heart surgery [31]. The solution is also frequently used for heart preservation in heart transplantation during the long-term ischemic period [32, 33]. On the other hand, the advantages of blood cardioplegia are that it is more physiologic; hemoglobin is used for oxygen transportation; it contains metabolic substrates and physiologic buffers; it provides good physiologic osmotic pressure; causes less hemodilution, and contains oxygen free radical scavengers. In addition, it has been shown that the blood cardioplegia is superior to crystalloid cardioplegia in cases over 1 h ischemia time [34–36].

The del Nido cardioplegic solution has been used widely in recent years due to the following advantages: It does not require frequently repeated administration (single dose is enough for up to 3 h) while providing myocardial protection similar to standard blood cardioplegia [37–39]. The del Nido solution has a 1:4 blood-to-crystalloid solution ratio [37]. So the hematocrit of the cardioplegic solution will be 7% in a patient with a hematocrit of 35%. The K^+ content of the del Nido solution is 24 mEq/L (blood + crystalloid component).

Table 87.3 Crystalloid components of del Nido cardioplegia solution

Component	Volume (mL)
Plasma-Lyte A base solution	1000
Mannitol 20%	16.3
Magnesium sulfate 50%	4
Sodium bicarbonate 8.4%	13
Potassium chloride (2 mEq/mL)	13
Lidocaine 1%	13

It is a modified depolarizing agent with lidocaine and Mg^{2+} added in the crystalloid component. The plasmalyte solution used for the del Nido preparation contains no Ca^{2+} (Table 87.3). The Ca^{2+} concentration of the del Nido solution is very low and only comes from its blood content. The del Nido solution is administered at a temperature of 8–12 °C as a single dose of 20 ml/kg (it is limited to 1 L in patients over 50 kg) in 1–2 min with an aortic root pressure of 100–200 mmHg. If the electrical activity is not reversed and the operation is not too long (up to 3 h) the cardioplegia is not repeated. In the cases of requiring short aortic cross-clamping (shorter than 30 min), such as atrial septal defect closure, after aortic declamping reactivation will be delayed, therefore the del Nido solution should be administered at a dose of 10 ml/kg [37].

In a study, it was shown that 38% of pediatric cardiac surgeons in North America were using del Nido solution [40]. Myocardial recovery is slow after classical cardioplegic solutions that contain high levels of K^+. Accumulation of high Na^+ and Ca^{2+} in cells is found to be responsible for this situation [41, 42]. Lidocaine (Na^+ channel blocker) and Mg^{2+} (Ca^{2+} competing agent) in the del Nido solution prevent this negative effect [37, 43, 44]. Since the del Nido solution does not require frequently repeated administration, it has a great advantage especially in newborns and infants, and in cases the aortic root is required to be opened.

Hypothermia

Hypothermia has been used since 1950 for myocardial protection to decrease oxygen requirements [3]. The methods to cool the heart are cold cardioplegia, systemic cooling with cardiopulmonary bypass, and topical myocardial cooling, which has the disadvantage of potential for phrenic nerve damage. However, the myocardial arrest is more important than hypothermia in myocardial protection. The arrested, normothermic heart requires 90% less oxygen than a normothermic working heart [45].

Hypothermia appears to have several detrimental effects, such as impaired mitochondrial and sarcoplasmic reticulum functions [46]. These effects lead to depletion of myocardial energy supplies. In 1989, Lichtenstein was the first to use normothermic continuous blood cardioplegia in a patient with complicated mitral valve replacement [47]. The patient had a posterior wall rupture, and the repair was successfully performed over 6 h of safe cross-clamp time. Soon after normothermic perfusion was used in adult cardiac surgery at the beginning of the 1990s, normothermic perfusion and cardioplegia started to be used in pediatric myocardial protection [48–51]. The most important advantage of normothermic blood cardioplegia is the preservation of the functions of sodium–potassium, ATPase, and calcium ATPase enzyme systems of the sarcoplasmic reticulum under normothermia [28, 36, 52]. Today, warm and cold blood cardioplegia are used in combination. In this technique, the aortic cross-clamp is applied, and the heart is arrested with the administration of warm cardioplegia, which is then switched to cold cardioplegia during induction. Throughout the cross-clamping, cold blood cardioplegia is repeated. The terminal warm blood cardioplegia is provided as a hot shot before removing the aortic cross-clamp [36, 53–55]. The advantage of terminal warm blood cardioplegia has been demonstrated in adult patients [56, 57]. However, studies regarding the advantages in pediatric patients are limited, and the results are conflicting [36, 55, 58].

Cardioplegia Administration Techniques

Antegrade, retrograde, and combined methods are used in cardioplegia delivery. Antegrade delivery is simple, and the cardioplegia is equally distributed to the coronary arteries. The disadvantage of the method is the risk of poor antegrade perfusion in the presence of aortic insufficiency and possible injury to the coronary ostia in an open aorta. Retrograde delivery has the disadvantage of having non-physiological and non-homogenous distribution, the risk of rupture of the coronary sinus, and decreased flow to the right ventricle and septum. It is advantageous in aortic insufficiency and aortic root surgery. Cardioplegia is used in single or multi-doses. Multi-dose cold cardioplegia is usually repeated about every 20 min [54, 55]. However, multi-dose warm cardioplegia is usually infused at shorter intervals [59].

Pump-assisted cardioplegia administration with minimal crystalloid addition to cardioplegia (minicardioplegia) was first described by Menasche in adult patients [60]. Minicardioplegia method was widely used in adult and pediatric patients thereafter [51, 61, 62]. The advantage of the minicardioplegia method is adding the ions (K^+ and Mg^{2+}) directly to the pump prime solution without adding any crystalloid to the cardioplegia solution (Fig. 87.1). Thus, hemoglobin level of cardioplegia delivered to the myocardium is not decreased, and also additional hemodilution caused by the cardioplegia drain from the coronary sinus to the pump is limited.

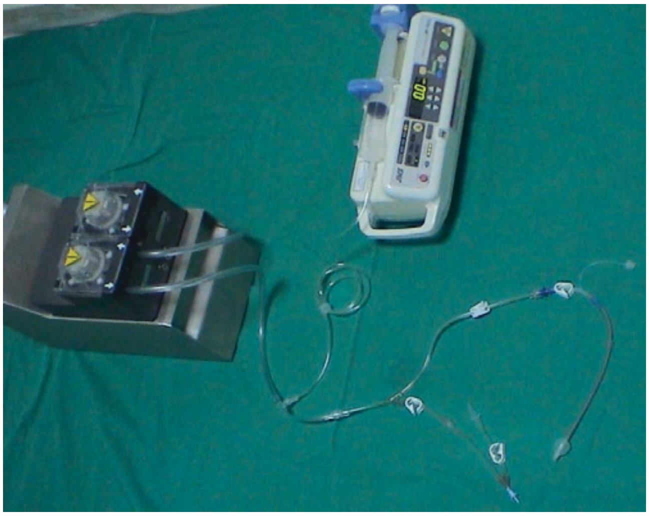

Fig. 87.1 Minicardioplegia set-up

Protection Strategies in Pediatric Myocardium

Poor myocardial protection is still considered as a significant cause for hospital mortality in children [28, 53]. Besides challenging myocardial protection, there are a lot of risk factors and situations that should be managed appropriately. Ventricular hypertrophy is a risk factor for inadequate myocardial protection. The hypertrophic ventricle is more sensitive to ischemia and is more negatively affected after prolonged aortic cross-clamp time.

Cardiopulmonary bypass (CPB) itself may negatively affect myocardium prior to aortic cross-clamping. Before starting CPB, an analysis of blood gases and ions should be obtained from the pump prime to ensure that they are within the physiological limits. Hyperkalemia (mostly due to old banked red blood cells used in the CPB priming), hypocalcemia (because of the citrate in the blood products), and acidosis must all be corrected before CPB initiation.

Initiating CPB without ligation of a functioning shunt or PDA or in cases of large aortopulmonary collateral arteries may negatively affect myocardial protection and also brain circulation. In such cases, steal of blood from aorta may cause hypotension, and excessive pulmonary venous return may cause ventricular distension. As a consequence, the pulmonary venous return may cause all cardioplegic solution to be washed away, and the return of electromechanical activity may occur. Therefore, in congenital heart diseases with excessive pulmonary venous return, it is important to place a left atrial vent early and provide effective decompression of the left ventricle. Early left ventricular/atrial venting is of great importance in preventing ventricular distension and pulmonary hemorrhage. If CPB is started without preparation of a vent catheter, immediate amputation of the left atrial appendage is an effective manoeuvre.

Rough manipulation and excessive retraction of heart, for exposure, may cause myocardial damage especially in newborns and infants and should be avoided. Instead, the use of multiple stay sutures to obtain adequate exposure is less traumatic in these age groups.

In cases of mitral valve repair and complete atrioventricular septal defect, the saline given to test the valves may lead to cardioplegia dilution with myocardial reactivation. Therefore, when testing for competence of the atrioventricular valves, the use of cardioplegia solution may prevent the reactivation.

Preischemic conditions, including cardiopulmonary resuscitation after cardiac arrest, cardiogenic shock or low cardiac output state, are also a risk factor for myocardial damage. Long aortic clamp time, ventricular distention, retraction, and ventriculotomy may lead to myocardial injury [63]. The risk of reperfusion injury following cross-clamping is high in cyanotic hearts. CPB should be instituted with a PO_2 of no greater than 200 mmHg to prevent oxidant-mediated re-oxygenation injury [53].

Coronary artery injury and air embolism to coronaries are risk factors for inadequate myocardial protection. Before removal of the aortic cross-clamp, complete deairing of the heart is very important. Remaining ventricular air bubbles can easily enter the right coronary artery which is usually located on the anterior aspect of the aorta. Once intracoronary air embolism occurs, it takes more time to remove the air from the coronaries of newborns and infants than in older age groups. In such circumstances, increasing aortic root pressure by adjusting the pump perfusion pressure helps to remove intracoronary bubbles. Also, in arterial switch operation, since both coronary ostia are transferred to the anterior side of the aorta, both coronary arteries are prone to air embolism. Temporarily occluding both coronary arteries with soft plastic bulldog clamps during 1–2 min after the removal of the aortic cross-clamp can prevent air embolism to these arteries.

Many factors can lead to post-operative low cardiac output syndrome such as hypocalcemia, acidosis, hypoxia, hyperkalemia, volume overloads (residual ventricular septal defect, pulmonary and aortic regurgitation), and pressure overloads (left and right ventricular outflow obstruction), mitral and tricuspid valve dysfunction, hypoplastic right or left ventricle, hypovolemia, pulmonary and systemic hypertension, cardiac tamponade, and rhythm changes. Transesophageal echocardiography is a valuable tool in identifying the etiology of low cardiac output after metabolic events are excluded. If there is low cardiac output syndrome and difficulty in weaning from CPB after a short aortic cross-clamp time (<60 min), the reason is probably a residual lesion or mechanical factors rather than myocardial dysfunction. However, if there is difficulty in weaning from the CPB after a long aortic cross-clamp time (over 120 min), myocardial dysfunction may be as responsible as residual lesions. Following a long aortic cross-clamp time, resting myocardium for 20–30 min on CPB provides safer weaning from CPB by reducing the harmful effects of prolonged ischemia, reperfusion and potassium.

Myocardial protection may be more challenging in cases such as long and complex operations in which repeated cardioplegia delivery from the open aortic root is required, newborn patients, or preoperatively damaged myocardium. If the morbidity and mortality rate is high particularly in long and complex procedures, revision of the myocardial protection method must be taken into account.

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Pediatric Extracorporeal Membrane Oxygenation and Mechanical Circulatory Assist Devices

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and Morgan K. Moroi

High Yield Facts

- Extracorporeal membrane oxygenation (ECMO) may serve as a bridge to recovery, heart or lung transplantation, destination therapy or long-term mechanical circulatory support (MCS).
- The overall survival rates (survived to discharge or transfer) for neonatal and pediatric ECMO support are 65.9% and 52.7%, respectively.
- Mortality rates are 12.6% for pulmonary support, 27.2% for cardiac support and 28.2% for extracorporeal cardiopulmonary resuscitation.
- Common complications of ECMO (occur >10% of the time) associated with low survival rate (<50%) include mechanical, neurologic, hemorrhagic and need for hemofiltration.
- There are three major devices that are currently used for short-term MCS in children: the RotaFlow, PediMag, and Tandem heart.
- According to the Pediatric Interagency Registry for MCS (Pedimacs) 71% of patients achieved a positive outcome with 88% of cardiomyopathy patients achieving a successful result following short-term MCS.
- Long term MCS can be in the form of ventricular assist devices (VADs) or total artificial hearts (TAHs).
- According to Pedimacs registry, overall survival of patients 6 months post VAD placement was approximately 72% and the older patients (age 11–19) had the highest survival (81%) compared to younger patients (less than 1 year) who had lower rates of survival (47%).
- Paracorporeal devices are associated with lower survival compared to intracorporeal devices.

Introduction

Extracorporeal membrane oxygenation (ECMO) and mechanical circulatory support (MCS) have become standard therapies for children with advanced cardiac and/or respiratory disease requiring high levels of support. Recent developments in device and circuit design, patient selection, and clinical management have permitted good outcomes even amongst small patients with complex disease [1–5]. This chapter will feature the indications, circuitry, management, complications, and current research relating to pediatric ECMO and MCS.

Pediatric Extracorporeal Membrane Oxygenation

Definition

ECMO is an extracorporeal technique modified from cardiopulmonary bypass (CPB) that provides prolonged cardiac and/or respiratory support using artificial devices in patients with heart and/or lung failure. ECMO may serve as a bridge to recovery, heart or lung transplantation, destination therapy or long-term MCS.

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Types

There are two main types of ECMO.

1. *Venoarterial ECMO (VA-ECMO)*: VA-ECMO drains venous blood from the right atrium or vena cava through the jugular or femoral vein, pumps it through an artificial lung (gas and heat exchange) and returns the oxygenated blood to either the right common carotid artery, ascending aorta (central ECMO) or femoral artery (peripheral artery). VA-ECMO provides full cardiac and pulmonary support, reduces myocardial effort, and reduces oxygen demand, allowing for myocardial and pulmonary recovery.
2. *Venovenous ECMO (VV-ECMO)*: VV-ECMO drains venous blood from the jugular or femoral vein, pumps it through an artificial lung, and returns the oxygenated blood to the right atrium through the femoral vein in larger patients or the jugular vein in smaller children. VV-ECMO supports only the respiratory system and does not provide cardiac support.

Additionally, there is a special type of ECMO, named pumpless extracorporeal lung assist (pECLA) that is also only able to provide respiratory support [6]. pECLA creates a femoral artery-to-femoral vein (FA-to-FV) or pulmonary artery-to-left atrium (PA-to-LA) shunt utilizing the arteriovenous pressure gradient and a low-resistance artificial lung to provide oxygenated blood without the use of a blood pump.

Indications and Contraindications

Indications for VA-ECMO

1. Pre-operative support, failure to wean from CPB, postoperative low cardiac output
2. Heart failure due to various causes, such as myocarditis, myocardial infarction, cardiomyopathy, pulmonary hypertension, intractable arrhythmias, sepsis
3. Cardiac arrest
4. Bridge to cardiac transplantation or ventricular assist device (VAD)

Indications for VV-ECMO

1. Hypoxic respiratory failure due to any cause, such as pneumonia, meconium aspiration syndrome (MAS), congenital diaphragmatic hernia (CDH), persistent pulmonary hypertension of the newborn (PPHN), acute respiratory distress syndrome (ARDS), severe air leak syndromes
2. Severe hypercapnia and acidosis
3. Bridge to lung transplantation

Contraindications for ECMO

1. Active bleeding or coagulation disorder
2. End-stage, irreversible cardiac, respiratory and neurologic disease, or multisystem organ failure
3. Unwitnessed cardiac arrest or prolonged cardiopulmonary resuscitation (CPR) (>60 min)
4. Aortic dissection, severe aortic valve regurgitation
5. Limited vascular access (for peripheral ECMO)

ECMO Circuit

A standard ECMO circuit consists of a blood pump, oxygenator (artificial lung), arterial cannula, venous cannula and tubing.

1. *Blood pump*: The blood pump functions as an artificial heart by moving blood through the ECMO circuit and delivering oxygenated blood to the patient. Blood pumps used for ECMO are typically either roller pumps or centrifugal pumps. Most roller pumps are occlusive and achieve blood flow by compression of the raceway to propel blood forward through the circuit. Because of the occlusive feature, a bladder reservoir (on the venous line) and servo-controlled pressure sensors (on the arterial and venous lines) are needed to prevent excessive positive pressure at the outlet of the pump and excessive negative pressure at the inlet of the pump.

   Centrifugal pumps are non-occlusive and use a magnetically driven impeller to generate flow. Flow depends on the rotational speed, preload and afterload of the centrifugal pump. New generation centrifugal pumps are currently preferred to roller pumps due to increased safety and less hemolysis (Table 88.1). Centrifugal pumps have also been recently developed to provide cutting-edge electrocardiography (ECG)-synchronized pulsatile flow [7–9]. ECG-synchronized pulsatile ECMO can create a pulse during diastole to increase coronary blood flow and maintain low flow during systole to reduce afterload to the heart [10, 11]. However, these pumps still require optimization for clinical use.
2. *Oxygenator*: The oxygenator serves as an artificial lung for gas exchange in the ECMO circuit. When selecting an oxygenator for use in an ECMO circuit, it is important to ensure that the expected blood flow within the circuit is lower than the maximal flow rate of the oxygenator, allowing for adequate oxygenation (Fig. 88.1). Hollow fiber membrane oxygenators with integrated heat exchangers are typically used for ECMO due to their low resistance, highly efficient gas and heat exchange, anti-plasma leakage, and easy priming. Furthermore, poly methyl pentene (PMP) diffusion membrane oxygenators are widely popular due to their stable performance in long-term ECMO support.
3. *Cannulae*: The vascular cannulae connect the ECMO circuit to the patient. There are a variety of cannulae com-

Table 88.1 The characteristics of ECMO centrifugal pumps

Blood pump	Thoratec PediMag centrifugal pump	Xenios i-cor diagonal pump	Thoratec CentriMag centrifugal pump	Maquet rotaflow centrifugal pump	Medtronic affinity CP centrifugal pump	Sorin revolution centrifugal pump
Priming volume (ml)	14	16	31	32	40	57
Revolution speed (rpm)	0–5500	0–10,000	0–5500	0–5000	0–4000	0–3500
Maximal flow rate (L/min)	1.5	8.0	10.0	9.9	10.0	8.0
Maximum outlet pressure (mmHg)	540	–	600	750	760	800
Inlet/outlet port (mm)	6.4	9.5	9.5	9.5	9.5	9.5

ECMO extracorporeal membrane oxygenation

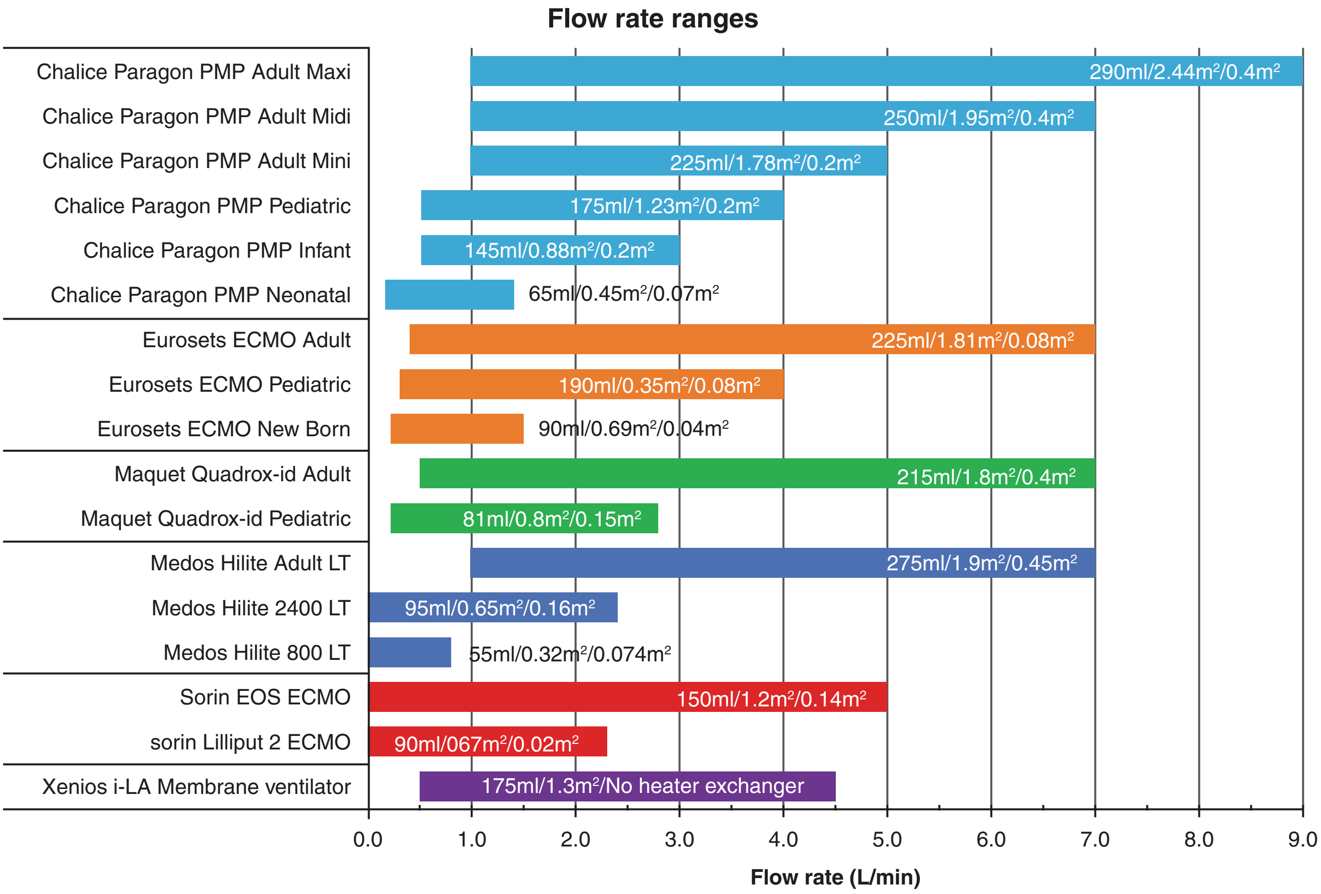

Fig. 88.1 Flow rate ranges of ECMO oxygenators (Priming volume/surface area of gas exchange/surface area of heat exchange)

mercially available for peripheral or central vascular access. For VA-ECMO, the arterial and venous cannulae are separately placed in the access sites. The size of the venous cannula is usually greater (by 2–4 French) than the arterial cannula. For VV-ECMO, two single lumen cannulae or one dual lumen cannula can be used. A dual lumen cannula allows for only one peripheral venous access point which simplifies the ECMO circuit and shortens the time of the cannulation procedure. The choice of the cannulae is made according to the mechanical and fluid characteristics (pressure drop, flow range, etc.) (Fig. 88.2).

4. *Tubing*: In the ECMO circuit, the tubing connects the blood pump, oxygenator and cannulae. The tubing is clear and made of medical grade polyvinylchloride (PVC), allowing it to be easily clamped or cut. The tubing is often coated with heparin, albumin, phosphorylcholine, or poly 2-methoxyethylacrylate (PMEA), etc. to improve

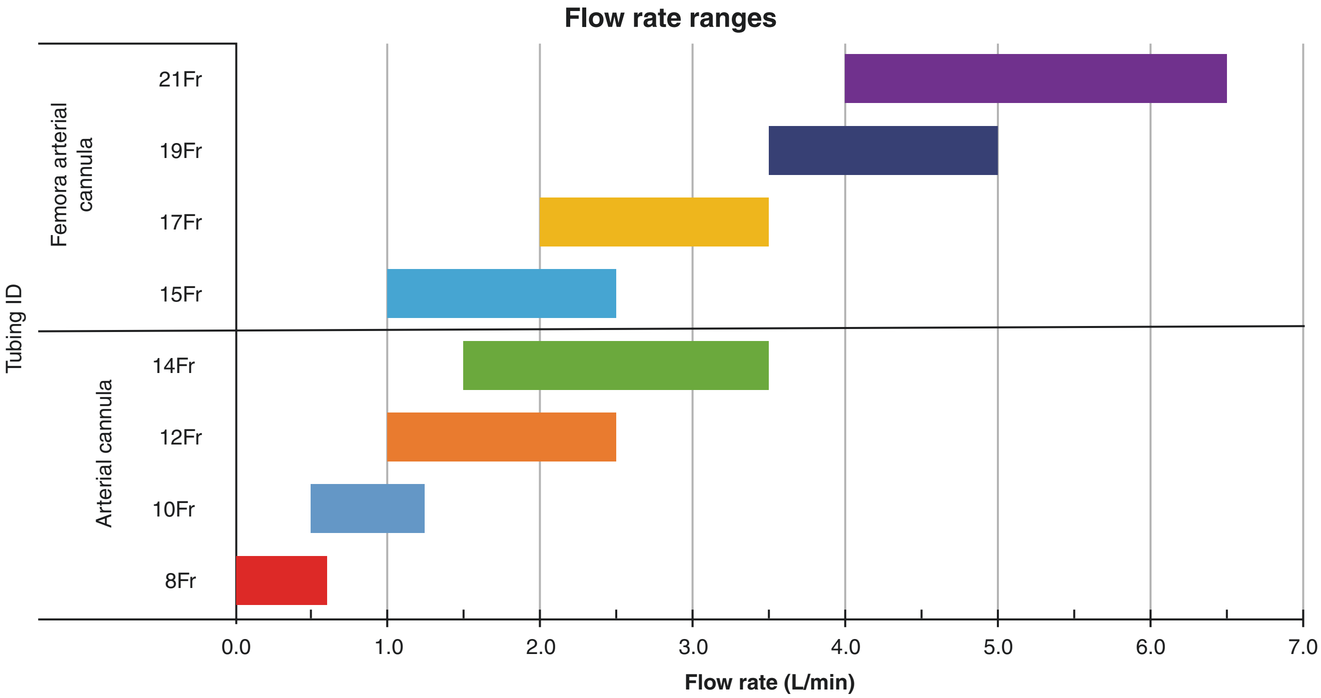

Fig. 88.2 Flow rate ranges of ECMO arterial cannulae

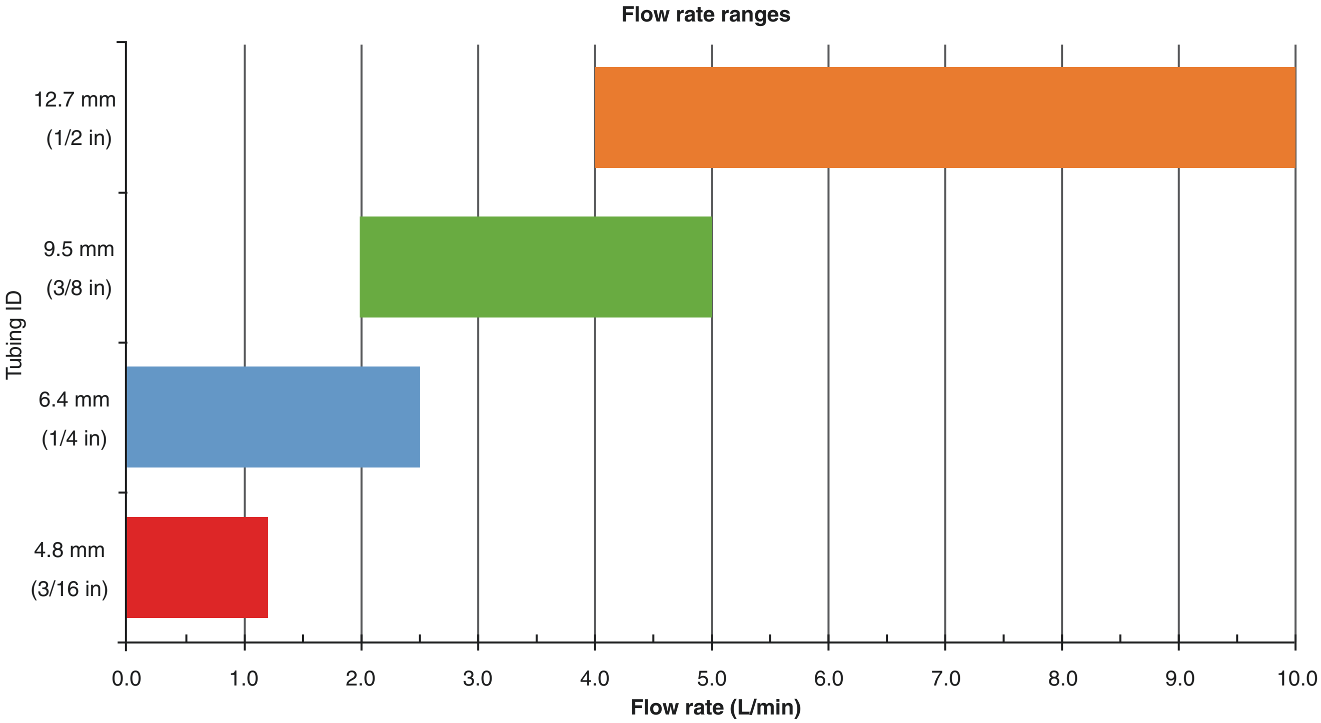

Fig. 88.3 Flow rate ranges of ECMO tubing based on 100 mmHg pressure gradient through 1 m of tubing

biocompatibility and prevent activation of the inflammatory response. Circuit tubing is available in inner diameter sizes of 4.8 mm (3/16 in.), 6.4 mm (1/4 in.), 9.5 mm (3/8 in.) and 12.7 mm (1/2 in.) (Fig. 88.3). Short tubing lengths are preferred as they can reduce circuit resistance, priming volume, heat loss and blood-contacting surface area. Many ECMO circuits also incorporate additional tubing to connect other beneficial components to the circuit. For example, pre-reserved side ports can be included to allow for blood sampling, medication infusion, or connection of other devices, such as a hemoconcentrator or continuous renal replacement therapy (CRRT).

5. *Others*: A bladder reservoir is commonly used in the venous line of the ECMO circuit when using a roller pump. Bladder reservoirs serve as an air trap and a pressure-servo regulator to prevent high negative pressures in the venous line. Additionally, continuous in-line oxygen saturation monitors can be used on the arterial and venous lines to monitor blood oxygenation efficiency of the oxygenator as well as the oxygen supply and demand of the patient. A continuous blood gas monitor may also be used to continuously measure blood parameters during ECMO.

Cannulation

1. *Access sites*: For newborns or infants, cervical or intracardiac cannulation is required. Neck cannulation involves fewer bleeding complications than open chest cardiac cannulation. The right common carotid artery and right internal jugular vein are common access sites for arterial and venous cannulation. In larger pediatric patients and teenagers, cannulation of the femoral artery and vein is also acceptable. In both age groups, a single-site, dual-lumen cannula inserted into the right internal jugular vein may be used for VV-ECMO. Open chest intracardiac cannulation may be more suitable for cardiac surgery patients who are unable to be weaned off of CPB.
2. *Insertion technique*: Percutaneous cannulation using the Seldinger technique is preferred by clinicians as it is associated with lower cannulation-related complications. Semi-Seldinger cannulation requires a small incision to insert the cannula under direct visualization. With this technique, there is no need for surgical arteriotomy or venotomy, and clinicians are better able to assess the vessels for proper selection of cannula size. Surgical cut-down cannulation also requires an incision to expose the vessels. However, this technique involves ligation of the proximal and distal vessels to control bleeding and a vertical incision on the vessel prior to the insertion of the arterial or venous cannula. If choosing to use the femoral artery as an access site, an additional reperfusion line should be placed to ensure distal limb perfusion as the femoral artery will be occluded by the cannula. An alternative approach to arterial cannulation is an open cut down technique with end-to-side vascular grafting to the artery to allow cannulation through the graft without obstructing the artery. In this case, a dual-lumen cannula is typically inserted into the internal jugular vein with the tip positioned in the low right atrium near the inferior vena cava ostium for VV-ECMO. Blood is drained from two drainage ports, one distally at the cannula tip and one proximally in the superior vena cava. The oxygenated blood is pumped into the right atrium towards the tricuspid valve through an infusion port located between the two drainage ports. Dual-lumen cannulae are placed percutaneously, and the position of the cannula is always verified with transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), or a combination of TEE and fluoroscopic guidance.

ECMO Management

1. *Priming solution*: Before connecting to the patient, the ECMO circuit is flushed with carbon dioxide and primed with crystalloid fluids, such as Plasmalyte or Ringer's lactate solution, for de-airing. Packed red blood cells (PRBCs) may be added to improve the hematocrit for the pediatric ECMO patient. Calcium, bicarbonate, heparin, plasma or albumin may also be added during priming procedure. Priming volume of the circuit is important as that volume is added to the patient's circulating blood volume and large priming volumes can lead to volume overload, especially in pediatric patients.
2. *Anticoagulation*: The blood must be anticoagulated before it comes into contact with the artificial surface of the ECMO circuit. Heparin is the most widely used anticoagulant for ECMO. Heparin prevents clot formation by binding and activating antithrombin III (ATIII), leading to the inactivation of certain clotting factors including thrombin (Factor IIa) and Factor Xa. Pharmaceutical grade heparin is derived from the mucosal tissues of pigs and cows and has a half-life of 60–90 min (unfractionated) to 4–5 h (low molecular weight). Typically, heparin is administered to the primed circuit (100 units/kg) and patient using an initial IV bolus dose of 30–100 units/kg, followed by a continuous intravenous infusion (10 and 30 units/kg/h). The activated clotting time (ACT) is regularly used to monitor anticoagulation effects (goal: 200–300 s) during ECMO. Apart from heparin, there are many other types of anticoagulants, including direct thrombin inhibitors, which are typically used when patients have a heparin or protamine allergy [12].
3. *Blood flow*: For VA-ECMO, optimal blood flow is achieved once the patient has an adequate mean arterial pressure (40–55 mmHg for neonates, 50–65 mmHg for pediatric patients, 60–80 mmHg for adults) with a mixed venous oxygen saturation (SvO_2) >65%, partial pressure of arterial oxygen (PaO_2) >60 mmHg, and partial pressure of carbon dioxide ($PaCO_2$) between 35 and 45 mmHg. Pump flow rates are usually 100–120 ml/kg/min for neonates, 80–100 ml/kg/min for pediatric patients and 60–80 ml/kg/min for adults. For VV-ECMO, adequate support is defined as an arterial oxygen saturation (SaO_2) greater than 80%, which can be achieved by adjusting ECMO flow, sweep gas flow and ventilator settings.
4. *Daily management*: Adequate sedation and analgesia are required for pediatric patients on ECMO. Mechanical ventilator settings are usually decreased for lung rest and

to decrease the risk of ventilator-associated lung injury after ECMO. Nutritional support as well as hematologic and fluid management is also important in the care of ECMO patients. A hemoconcentrator or hemofilter may be used to remove excessive fluid, cytokines and wastes from the ECMO circuit. Pre-/post-oxygenator pressures and venous line pressure are routinely monitored. Blood gases, plasma free hemoglobin and ACT may be measured every day or as needed.

5. *Weaning off ECMO*: Decannulation is considered once the patient's native heart and lungs are able to maintain satisfactory cardiopulmonary stability. Prior to decannulation, the ECMO flow is gradually decreased and once deemed ready for decannulation, the circuit tubing is clamped and the blood pump is turned off if using a centrifugal pump. Alternatively, if using a roller pump, the blood pump is first turned off prior to clamping the circuit tubing. Inotropic and ventilatory therapy is reestablished. Heparin is discontinued. ECMO cannulae are removed.

Complications

ECMO can support respiratory and/or cardiac systems, but it also leads to various complications. Common complications (occur >10% of the time) associated with low survival rate (<50%) are shown in Table 88.2 [13]. All complications are associated with increased morbidity and mortality in ECMO patients. Therefore, the continual development of circuit components and patient management is critical in order to reduce the rates of these detrimental ECMO-related complications.

Clinical Outcomes

According to the international summary produced by the Extracorporeal Life Support Organization (ELSO) in January 2018, the overall survival rates (survived to discharge or transfer) for neonatal, pediatric and adult patients were 65.9%, 52.7% and 47.8%, respectively [14]. Survival rates for patients requiring pulmonary support, cardiac support

Table 88.2 Common complications (Only incidence rate ≥10%, survival rate <50%) for ECMO patients (Data from ELSO registry during 2012 to July 2017)[a]

Complication	Respiratory			Cardiac			ECPR		
	Neonatal	Pediatric	Adult	Neonatal	Pediatric	Adult	Neonatal	Pediatric	Adult
Case (n)	4366	2886	10,225	2357	3418	9993	763	1943	3231
Mechanical									
Clot oxygenator				12% (38%)	10% (48%)				
Clot other				16% (41%)	14% (46%)		15% (34%)		
Hemorrhagic									
Cannulation site bleeding				12% (36%)		16% (38%)	13% (31%)	18% (39%)	15% (32%)
Surgical site bleeding				23% (34%)	22% (49%)	17% (32%)	19% (33%)	12% (43%)	
Hemolysis	14% (46%)			14% (22%)	10% (35%)		14% (21%)		
Neurologic									
CNS hemorrhage by US/CT	12% (39%)			13% (26%)			15% (29%)		
CNS infarction by US/CT								11% (25%)	
Renal									
Creatinine 1.5–3.0						20% (37%)			18% (27%)
Creatinine >3.0						10% (31%)			10% (28%)
Hemofiltration required				26% (34%)	24% (45%)	11% (33%)	27% (37%)	22% (41%)	12% (27%)
CAVHD required		12% (38%)	11% (47%)			13% (29%)			10% (22%)
Cardiovascular									
Inotropes on ECMO				47% (37%)		46% (38%)	48% (37%)	44% (38%)	
Cardiac arrhythmia				12% (30%)		14% (35%)	11% (25%)	13% (42%)	
Hypertension requiring vasodilators				12% (46%)			15% (41%)		
Infectious									
Culture proven infection					10% (43%)	11% (39%)			10% (36%)
Metabolic									
Glucose >240 mg/dl		10% (49%)		11% (35%)		11% (42%)	18% (37%)	14% (34%)	16% (27%)
pH <7.20		11% (41%)					14% (28%)	14% (22%)	15% (16%)

Data are percent reported (percent survived)

CNS central nervous system, *CAVHD* continuous arteriovenous hemodialysis, *CT* computer tomography, *ECMO* extracorporeal membrane oxygenation, *ECPR* extracorporeal cardiopulmonary resuscitation, *ELSO* Extracorporeal Life Support Organization, *US* ultrasonography

[a] Adapted from [13]

and extra-corporeal cardiopulmonary resuscitation (ECPR) were 66.8%, 45.1% and 36.0%, respectively. Mortality rates were 12.6% for pulmonary support, 27.2% for cardiac support and 28.2% for ECPR even after patients were successfully weaned off ECMO.

Translational Research for Optimization of Neonatal and Pediatric ECMO Circuitry

1. *Pulsatile ECMO*: ECMO pumps currently used in practice consist of rotary and roller pumps. The non-pulsatile flow generated by these pumps mixes with the flow generated by the patient's native heart to provide systemic perfusion. However, these pumps are also associated with weakening the circulatory pulsatility, a complication associated with increased afterload and aortic insufficiency in adult patients. It is hypothesized that similar effects would also occur in neonatal and pediatric patients. To combat this, ECMO pumps are now able to provide pulsatile flow.

   Diagonal pumps have been shown to produce physiologic-like flow, deliver more hemodynamic energy, and create less systemic inflammation when compared to roller pumps that produce non-pulsatile flow. While this is an improvement over standard roller pumps, diagonal pumps are unable to synchronize pulses with the patient's heartbeat, allowing for the formation of canon waves and limiting the maximal amount of hemodynamic energy delivery.

   Recently, a novel system has been devised to provide electrocardiogram (ECG)-synchronized pulsatile flow. By detecting R-waves of the ECG signal, this pump is able to deliver pulses during diastole to avoid the formation of canon waves and deliver more hemodynamic energy to the patient. This pump would also allow the flow to be modulated by the patient's autonomic nervous system, which is more physiologic than a preset rate. While this pump is seeking Food and Drug Administration (FDA) approval, it has been demonstrated in vitro that the pump is capable of producing adequate non-pulsatile and pulsatile flow for neonatal and pediatric ECMO. The pulsatile settings of this pump include pulsatile amplitude, frequency, and width, and these settings were found to greatly impact the quality of pulsatility generated by the pump. Furthermore, a pulsatile amplitude of 2000–3000 rpm was shown to achieve physiologic-like pulsatility [9]. Still, in vivo studies are needed to classify this pump in a more clinical setting (Fig. 88.4).
2. *ECMO with hemoconcentrators*: Translational research done at Penn State Children's Hospital compared the use of different hemoconcentrators added into neonatal ECMO circuitry. This evidence-based research is necessary to optimize the ECMO circuitry for neonates in order to improve outcomes and prevent complications. Hemofiltration is used during neonatal extracorporeal life support (ECLS) to prevent acute kidney injury and fluid overload and can be done with an in-line hemoconcentrator. The in vitro study compared three different Hemocor hemoconcentrators in two different neonatal ECMO circuits with a Quadrox-iD pediatric oxygenator, one with a Maquet H20 Roller Pump and one with a Maquet RotaFlow centrifugal pump, at different pressures and flow rates with human blood [15]. The three hemoconcentrators used were Hemocor HPH 400, Mini, and Junior. The Hemocor HPH 400 is the largest, the Mini is the smallest with the lowest priming volume, and the Junior has a similarly low priming volume but has larger ultrafiltration potential. Information about the circuit components is listed in Table 88.3.

   Results of this study demonstrated that the roller and centrifugal pumps performed similarly in terms of circuit pressures, blood flow diverted through each hemoconcentrator, pressure drop across circuit components, and total hemodynamic energy (THE) delivered to the patient which is used as a measurement of total body organ perfusion. In terms of the various hemoconcentrators, the Hemocor HPH Junior added the most resistance to the circuit and the Hemocor HPH 400 added the least resistance to the circuit as demonstrated by amount of blood flow diverted through, and the pressure drop across the hemoconcentrator.

   While the hemoconcentrators added different amounts of resistance to the circuit, the amount of hemodynamic energy delivered to the patient as measured by the THE after the arterial cannula were similar for each hemoconcentrator due to stable pseudo-patient pressure. Future in vivo studies can further define the function of these three hemoconcentrators in terms of ultrafiltration ability while maintaining THE delivery to the patient.
3. *ECMO with continuous renal replacement therapy*: It is estimated that 19.3% of neonates receiving respiratory support and 41.8% of neonates receiving cardiac support need CRRT during the course of their ECMO treatment [16].

Table 88.3 The components of the experimental circuit

Item	Component		
Hemoconcentrator	**Hemocor HPH 400**	**Hemocor HPH Mini**	**Hemocor HPH Junior**
Membrane surface area (M^2)	0.3	0.07	0.09
Priming volume (mL)	34	14	8
Pressure drop (mmHg)	61	30	55
Internal unit diameter (cm)	3.0	2.5	2.5
Internal fiber diameter (µm)	200	620	200
Pump	**Maquet H20 Roller Pump**	**Maquet RotaFlow Centrifugal Pump**	
Flow range (L/min)	0–10	0–10	
Maximum pressure (mmHg)	997	750	
Rotational speed range	0–250 rpm	0–5000 rpm	
Oxygenator	**Quadrox-iD Pediatric Oxygenator**		
Blood flow range (L/min)	0.2–2.8		
Priming volume (mL)	81		
Gas exchange surface area (m^2)	0.8		

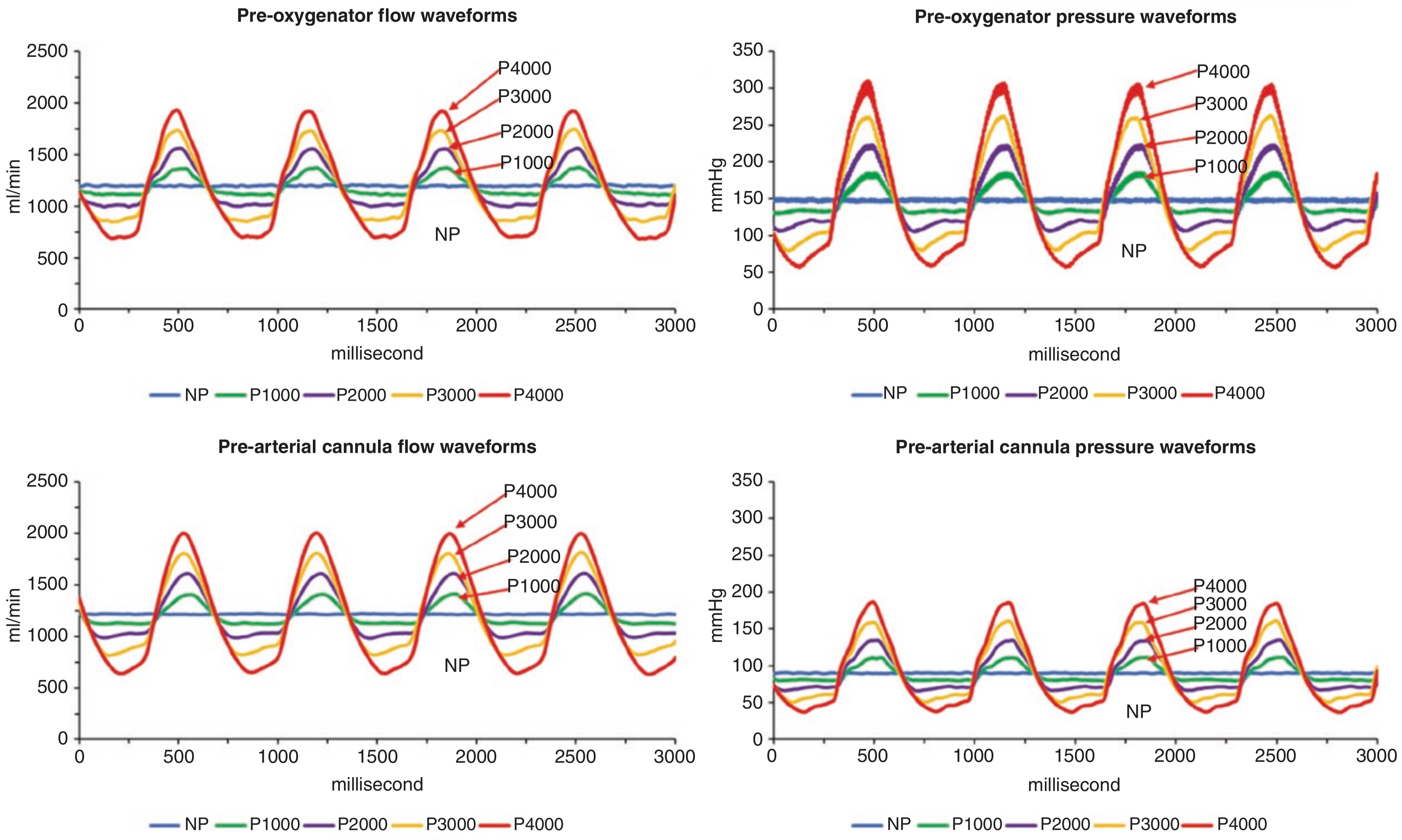

Fig. 88.4 Flow and pressure waveforms for pediatric circuit at 1200 mL/min with pseudopatient pressure 60 mmHg under non-pulsatile (NP) and pulsatile (P) mode with pulsatile amplitude 1000–4000 rpm. (Reproduced with permission from [9])

> The need for hemofiltration may be a consequence of the ECMO system itself as the exposure of blood to artificial surfaces can lead to the activation of hemolysis, the coagulation cascade, and the systemic inflammatory response, causing acute kidney injury. Additionally, there are many other complications, such as electrolyte disturbances and fluid overload that can incite the need for CRRT during ECMO. Therefore, as it is common for neonatal patients on ECMO to subsequently require CRRT and as neonates lack the insertion sites needed to operate two extracorporeal circuits, inclusion of CRRT into the ECMO circuit may provide advanced treatment for this population.

Recent studies have assessed the effects of inserting CRRT into the ECMO circuit. Research conducted by Profeta et al. examined the hemodynamic performance of various combined ECMO and CRRT circuits that included the CRRT component at seven different positions (Fig. 88.5) [17]. The study concluded that, in ECMO circuits with a centrifugal pump, CRRT could be included at any position in the ECMO circuit without having significant effects on the circuit hemodynamics. However, CRRT location was found to have a significant impact on hemodynamics in ECMO circuits that utilized roller pumps. Position A did not exhibit significant changes in flow, pressure, or hemodynamic energy compared to the ECMO circuit without CRRT. Positions B, C, D, E, F, and G all either exhibited changes in flow rate, increases in pressure drop, and/or decreased the amount of hemodynamic energy delivered to the patient. The authors recommended the use of CRRT position A due to its hemodynamic similarities to the ECMO circuit without CRRT.

Research done by Shank et al. at Penn State Hershey Children's Hospital examined the addition of CRRT in a neonatal ECLS circuit in order to optimize the use of hemofiltration to prevent kidney damage without requiring a separate access site in the smallest of patients [18]. The study looked at a neonatal ECLS circuit including a Maquet RotaFlow centrifugal pump or a Maquet HL20 roller pump with a Quadriox-iD pediatric oxygenator with a CRRT circuit introduced at different inlet and outlet positions (Fig. 88.6). CRRT position A had blood entering CRRT between the pump and the oxygenator, position B had the blood recirculated through the pump, and position C had blood bypassing the pump. An Emboli Detection and Classification (EDAC) system was used to detect gaseous microemboli throughout the circuit and hemodynamic data was collected.

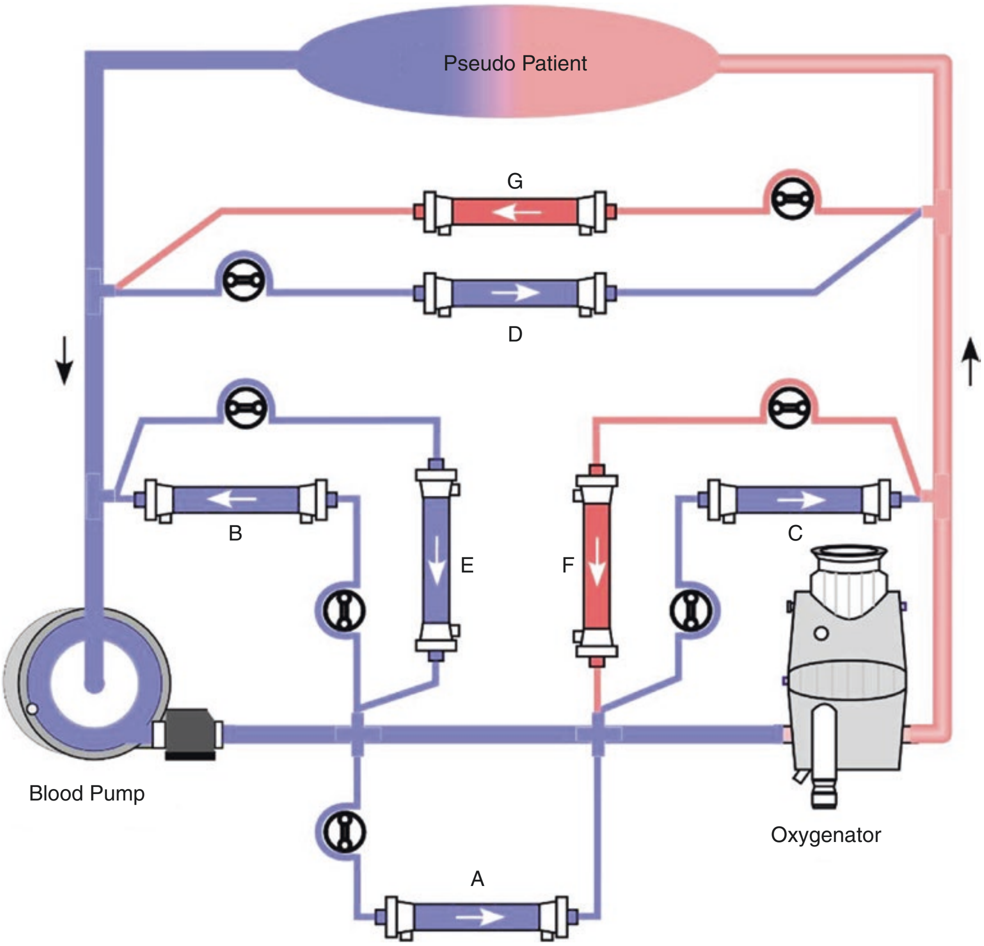

Fig. 88.5 Seven continuous renal replacement therapy (CRRT) positions within the ECLS circuit. (Reproduced with permission from [17])

Results of this study demonstrated that CRRT at any position with the centrifugal pump had similar flow rates, mean pressures, and total hemodynamic energy loss compared to no CRRT. With the roller pump, however, position C demonstrated increased flow rates, decreased mean pressure, higher pressure drop across the oxygenator, and higher total hemodynamic energy loss compared to the same circuit without CRRT. Position C also demonstrated poor gaseous microemboli handling with the roller pump. This data suggests that in contrast to positions A and B that had minimal differences in hemodynamic performance and gaseous microemboli handling compared to without CRRT, position C is unsafe for addition of CRRT and is not recommended for clinical use. This information is important and immediately translatable research that will help to better optimize the safety and efficacy of neonatal ECLS with in-line hemofiltration.

Summary

Pediatric ECMO is effective for short-term circulatory and respiratory support as well as bridging to hospital discharge, heart and/or lung transplantation, or long-term MCS. There are two modes of ECMO, venoarterial and venovenous. Venoarterial ECMO supports heart and lung function, whereas venovenous ECMO solely supports lung function. ECMO management typically entails anticoagulation, sedation and analgesia for patient comfort, nutritional support, and pressure and flow monitoring of the ECMO circuit. The ECMO circuit consists of the blood pump, oxygenator, cannulae, and tubing, all of which can be optimized for hemodynamic performance. Translational research can be used to optimize ECLS circuitry for purposes such as pulsatile ECMO, hemoconcentration, and CRRT [9, 15, 17]. Further optimization of pediatric ECMO devices, implantation technique, and clinical management may help clinicians further improve the survival rate in neonates, infants and children with reversible cardiac and/or respiratory failure.

Pediatric Mechanical Circulatory Assist Devices

MCS for pediatric patients with heart failure has a short history given that the first pediatric specific VADs were only first made available in 2000 [19]. Despite this, there is a large

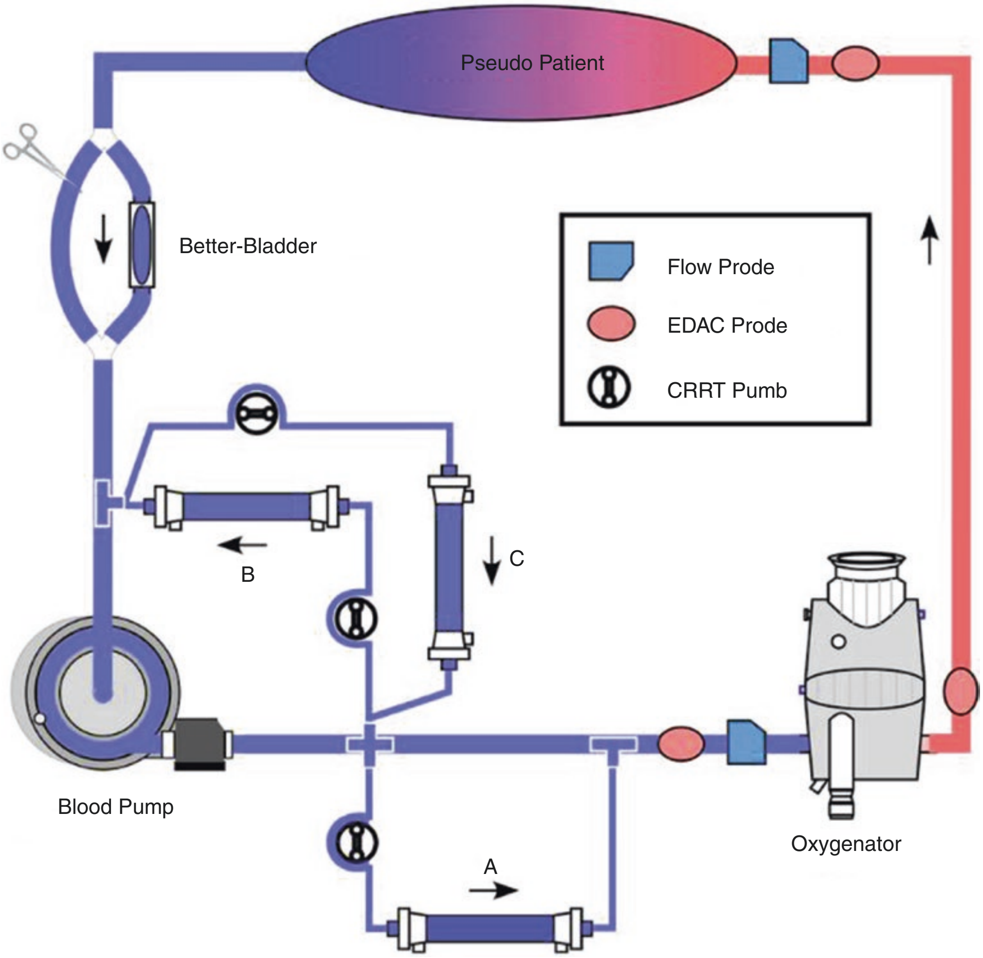

Fig. 88.6 Three CRRT positions in a simplified extracorporeal life support circuit. (Reproduced with permission from [18])

and expanding population of children living with heart failure [19, 20]. Heart transplantation has been the standard of care for these patients [21]. However, unlike their adult counterparts, children with heart failure compensate well and typically do not have symptoms until they progress to end-stage disease, making it difficult for these patients to safely await transplantation [19]. Many of these critically ill children were originally bridged to transplantation with ECMO, but this yielded poor outcomes [22]. With this in mind, strides have been made in developing MCS devices to support children as a bridge to recovery, decision, or transplantation. This section will discuss currently available options for short and long-term MCS support for neonatal and pediatric patients with end-stage heart failure.

Short-Term Pediatric MCS

Patient selection and timing of MCS is critical for successful outcomes [19]. Short-term devices are typically used in patients with acute processes requiring a bridge to recovery. Additionally, patients may be placed on short-term MCS as a bridge to decision when it is clinically unclear if a patient should be initially placed on long-term MCS.

Devices

Device selection is also critical for obtaining good results. Factors that contribute to this decision include: the site requiring support, length of support, and devices available. Given that device options are fairly limited, this variable typically dictates device selection. There are three major devices that are currently used for short-term MCS in children: the RotaFlow, PediMag, and Tandem heart (Fig. 88.7).

Jostra Rotaflow centrifugal pump: The Jostra Rotaflow centrifugal pump is a temporary ventricular assist device (VAD) capable of supporting both adult and pediatric patients. It is a centrifugal extracorporeal pump made of polycarbonate that is powered by an electromagnetic mechanism that produces laminar flow and reduces friction and hemolysis. The pump is 50 mm in diameter, has a 32 mL priming volume, and has a maximal continuous flow rate of 10 L/min (Table 88.1). A membrane oxygenator may be attached to this circuit at any point to convert this circuit into an ECMO circuit.

Thoratec PediMag: The Thoratec PediMag is an extracorporeal temporary VAD designed specifically for pediatric patients (Table 88.1). The pump is indicated in patients as small as 3 kg with a body surface area (BSA) of less than 1.3 m^2 and estimated support time of less than 2 weeks. The device is magnetically levitated, lessening friction and hemolysis, and capable of producing continuous flow rates of up to 1.5 L/min. The PediMag is connected to the patient through central cannulation, and an oxygenator may also be inserted into this circuit to create an ECMO circuit, if needed.

Tandem Heart: The Tandem Heart is an extracorporeal pediatric VAD that can be utilized in patients >40 kg with BSA >1.3 m^2 and an estimated recovery time of less than 2 weeks. The device consists of a hydrodynamic fluid bearing that supports a spinning rotor that provides continuous flow rates of up to 5 L/min. The Tandem Heart is percutaneously placed via the femoral vessels using an arterial cannula to access the femoral artery and an extended trans-septal cannula to puncture the interatrial septum and access the left atrium. For children under 70 kg, a vascular graft is typically sewn onto the femoral artery to protect the native artery and preserve blood flow to the distal limb.

Outcomes and Complications

Little data are available with regards to outcomes of children supported by short-term devices. However, the Pediatric Interagency Registry for MCS (Pedimacs) recently published an article examining the outcomes of children support by devices labelled for "temporary use" [23]. The study assessed 63 pediatric patients at 20 centers with a median age of 3.7 years (range <1 day to 18 years). The underlying

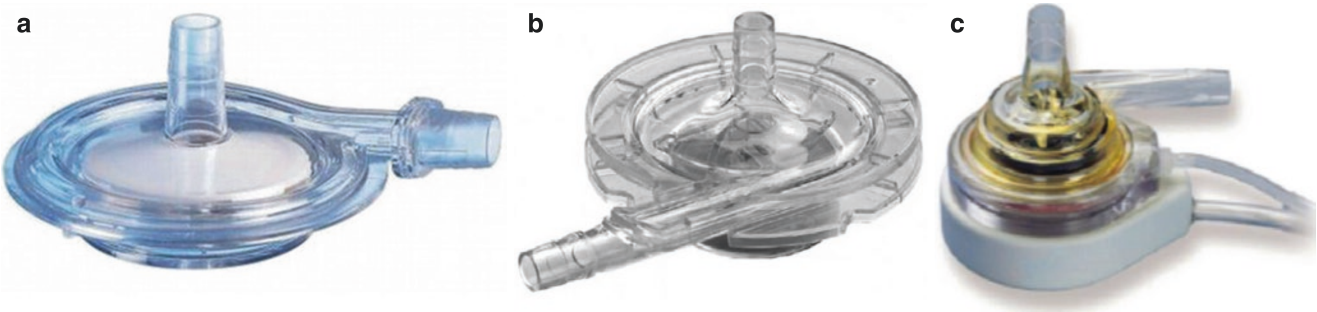

Fig. 88.7 (**a**) RotaFlow pump head (Courtesy of Maquet Cardiovascular). (**b**) PediMag pump head (Courtesy of Thoratec Co.). (**c**) Tandem Heart pump head (Courtesy of Cardiac Assist Inc.)

diseases requiring support included: congenital heart disease (41%), cardiomyopathy (40%), and myocarditis or rejection (19%). Median duration of support was 15 days (range <1–227 days). Common complications were bleeding (29%) and neurologic dysfunction (24%). As a result, 30% of patients achieved a bridge to recovery, 17% progressed to transplantation, 2% remained alive on device, and 22% successfully transitioned to durable VAD. Overall, 71% of patients achieved a positive outcome with 88% of cardiomyopathy patients achieving a successful result. While outcomes have improved with a majority of patients achieving successful outcomes, these results may continue to improve as pediatric short-term MCS use, development, and clinical experience continues to grow.

Long Term Pediatric MCS

Long term MCS can be in the form of VADs or total artificial hearts (TAHs).

Implantable VADs improve health outcomes in patients with heart failure who might not otherwise survive and there is enough research to show that they can be successfully used as a bridge to transplantation or recovery or as a destination therapy. Implantable VADs can come in the form of left ventricular, right ventricular, or biventricular assist devices (LVADS, RVADs, BiVADS). LVADs are most commonly used to support left ventricular function and they are used to bridge patients to transplantation while waiting for a heart to become available or in reversible conditions like post-cardiotomy cardiogenic shock [24]. Their use as destination therapy in patients with end stage heart disease who are not transplant candidates is more recent, but research shows it is successful at improving health outcomes [25–30]. Some FDA approved VADs include the HeartMate II LVAD (Thoratec Corp.), the Thoratec LVAD (Thoratec Corp.), Levitronix Centrimag RVAD (Levitronix, LLC), DeBakey VAD Child (MicroMed Technology, Inc.), EXCOR pediatric BiVAD (Berlin Heart, Inc.), and the HeartWare VAD (Heartware Intl., Inc.). Information about these devices and their use is listed in Table 88.4.

TAHs improve survival and quality of life for patients in some clinical scenarios and research shows they can be used as a bridge to transplantation. There is not yet enough research to prove that TAHs are successful in improving health outcomes for patients when used as a destination therapy and this use is still under investigation [26]. Some TAHs that are FDA approved include the SynCardia Temporary TAH (SynCardia Systems, Inc.) and the AbioCor TAH (AbioMed, Inc.). More information about the use of these devices is listed in Table 88.4.

Pediatric Interagency Registry for Mechanical Circulatory Support (Pedimacs)

The Pedimacs collects data relevant to the use of VADs in pediatric patients under 19 years old. The most recent Pedimacs report from January 2018 summarizes data on VAD use in pediatric patients from September 2012 to September 2016. During this time 42 hospitals in the United States implanted 432 VADs in 364 patients [31]. Of these children, 59% were under 1 year old, 18% were between the ages of 1–6 years old, 15% were 6–10 years old, and 48% were 11–19 years old. The pre-implant diagnosis varied between the patients but 61% of them had cardiomyopathy (93% of these were dilated cardiomyopathy), 11% had myocarditis, and 21% had congenital heart disease. The most common indication for VADs in these patients was bridge to transplantation with 81% of the patients either listed for transplant or likely to be listed for transplant at the time of implantation [31].

Devices and Patients

The devices used for MCS for these patients were organized by design and flow characteristics. Intracorporeal continuous flow devices were the most commonly used followed by paracorporeal pulsatile flow devices. Paracorporeal continuous flow, percutaneous VADs, and TAHs were used less frequently. The choice of device implantation was greatly impacted by size limitations in the pediatric population. The paracorporeal pulsatile and continuous flow devices were used in patients with a median age of 1.7 years [31]. The intracorporeal continuous flow devices were used in patients with a median age of 14.9 years. Paracorporeal devices were preferred for patients under 6 years old and intracorporeal was preferred for patients over 6 years old [31].

Survival Post-VAD Implantation

Overall survival of patients 6 months post VAD placement was approximately 72% and the older patients (age 11–19) had the highest survival (81%) compared to younger patients (less than 1 year) who had lower rates of survival (47%) [31]. Paracorporeal devices were associated with lower survival compared to intracorporeal devices which is likely explained by paracorporeal devices being used in younger and sicker patients and intracorporeal devices being reserved for the older and more stable patients. Because of this important confounding variable, the effect of device type on survival is

Table 88.4 FDA approved ventricular assist devices and total artificial hearts used for long term mechanical circulatory support

Ventricular assist devices		
	Device:	HeartMate II (Thoratec Corp.)
	Type:	LVAD
	Use:	Bridge patients to transplant or as a destination therapy
	Device:	Levitronix Centrimag
	Type:	RVAD
	Use:	Temporary circulatory support post-cardiotomy

(continued)

Table 88.4 (continued)

Ventricular assist devices		
	Device:	DeBakey VAD Child (MicroMed Technology, Inc.)
	Type:	LVAD
	Use:	Bridge to transplant in pediatric patients
	Device:	EXCOR Pediatric System (Berlin Heart, Inc.)
	Type:	BiVAD
	Use:	Bridge to transplant in pediatric patients including newborns up to teenagers
	Device:	HeartWare Ventricular Assist System (Heartware Intl., Inc.)
	Type:	VAD
	Use:	Bridge to transplant
Total artificial hearts		

Table 88.4 (continued)

Ventricular assist devices		
	Device:	SynCardia Temporary TAH (SynCardia Systems, Inc.)
	Type:	Temporary TAH
	Use:	Bridge to transplant
	Device:	AbioCor TAH (AbioMed, Inc.)
	Type:	Implantable TAH
	Use:	Destination therapy

unclear. Pre-implantation diagnosis had an impact on survival post-VAD placement. Six-month survival was higher for patients with cardiomyopathy compared to congenital heart disease (67% vs. 45%) [31].

Adverse Events

Of the 364 patients who had a VAD implanted, 73 patients died after implantation with neurologic dysfunction and multisystem organ failure being the most common causes of death [31]. A total of 1055 adverse events were reported in the Pedimacs registry and these events included infection, bleeding, and neurologic events. At least one adverse event occurred in 58% of patients with more adverse events happening in younger patients (under 5 years old).

Summary

Pediatric MCS has been used as bridge to transplant or recovery for children with end-stage heart failure due to a variety of causes including cardiomyopathy, myocarditis, and congenital heart disease. With further research and development, many advancements have been made in pediatric MCS [19–21]. Current data on pediatric MCS use and outcomes are reported in the Pedimacs MCS Registry. Although pediatric MCS has had many great successes, adverse events do occur. Improvement in device miniaturization, biocompatibility and durability are areas of ongoing development in pediatric MCS.

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Palliative Operations for Congenital Heart Disease

89

Masakazu Nakao and Roberto M. Di Donato

High Yield Facts

- Palliations for congenital heart anomalies are surgical procedures meant to offset major hemodynamic derangements, usually in preparation for staged repair. They alleviate symptoms but cannot prevent the natural progression of the disease.
- Palliative surgery can be the definitive treatment for certain borderline conditions.
- The procedure to decrease pulmonary blood flow is pulmonary artery banding, either of the main pulmonary artery or of its branches.
- The procedures to increase pulmonary blood flow include classic and modified Blalock-Taussig shunt, central shunt, bidirectional Glenn shunt, right ventricle-to-pulmonary artery shunt and others.
- The procedures to enhance atrial mixing are either trans-catheter balloon atrial septostomy or surgical atrial septectomy.
- Hybrid palliation for hypoplastic left heart syndrome or similar conditions is a valid alternative to a primary Norwood operation.

Introduction

Palliations for congenital heart anomalies are surgical procedures meant to offset major hemodynamic derangements in alternative and/or in preparation to repair. Generally inept to prevent the natural progression of the disease, they do alleviate symptoms and, occasionally, may serve as definitive therapeutic solutions. Although mostly abandoned due to advances in corrective neonatal heart surgery, palliations are still performed in some high-risk cases or as planned first step towards a staged repair (e.g. in the case of single ventricle conditions). Usually adopted in infants, they tackle specific cardiovascular problems by different mechanisms, including: (1) reduction of pulmonary blood flow; (2) increase in pulmonary blood flow; (3) increase in atrial mixing; (4) other. Noteworthy, only few repairs, e.g. closure of atrial and/or ventricular septal defects, restore a truly normal and lasting cardiac condition. Most commonly, the distinction between corrections and palliations is rather academic. This is particularly true of the so called "physiologic" (as opposed to "anatomic") repairs, e.g. those relying either on a single ventricle (Fontan operation) or on a systemic right ventricle (atrial switches and repair of congenitally corrected transposition of the great arteries).

Procedures to Decrease Pulmonary Blood Flow

Pulmonary Artery Banding

Banding of Main Pulmonary Artery

Pulmonary artery banding was introduced by Muller and Danimann in 1951 to manage heart anomalies with increased pulmonary blood flow [1]. By reducing pulmonary blood flow and pressure, banding helps in controlling congestive heart failure and preventing pulmonary vascular obstructive disease. Furthermore, by imposing a pressure overload, it may stimulate hypertrophy of the underlying ventricle (especially in the presence of an intact ventricular septum).

Indications

a) *Reduction of pulmonary overflow* in conditions with severe left-to-right shunt at ventricular level, e.g. multiple ventricular septal defects ("Swiss-cheese" type) or single ventricle hearts [2]. In extremely low birth-weight infants,

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risks and benefits of banding must be weighed against corrective surgery.

b) *Retraining of left ventricle* in preparation for "anatomic" repair for biventricular conditions with failing systemic right ventricle and no ventricular communication, e.g. late simple transposition of the great arteries (>6 weeks of age) [3], failing atrial switch operation [4] and congenitally corrected transposition of the great arteries [5, 6].

Technique

Pulmonary artery banding is achieved through either a left lateral thoracotomy or a median sternotomy. A thoracotomy preserves the mediastinum for later open-heart repair. However, a median sternotomy is a safer option in neonates with complex congenital cardiac anomalies.

A pressure line is, first, inserted in the pulmonary artery confluence. The main pulmonary artery is, then, surrounded by a band that is passed through the transverse sinus (from right to left), retrieved in between the great arteries and fixed as a closed loop. The band circumference is pre-measured according to the "Trusler rule": 20 mm + 1 mm/kg body weight for simple defects and 24 mm + 1 mm/kg body weight for single ventricle physiology [7]. The tightening is subsequently adjusted making sure to maintain pulsatile pulmonary artery pressure (lower than half aortic systolic pressure) with systemic oxygen saturation ≥80%, while avoiding bradycardia. Finally, the band is secured in place to prevent distal migration (Fig. 89.1).

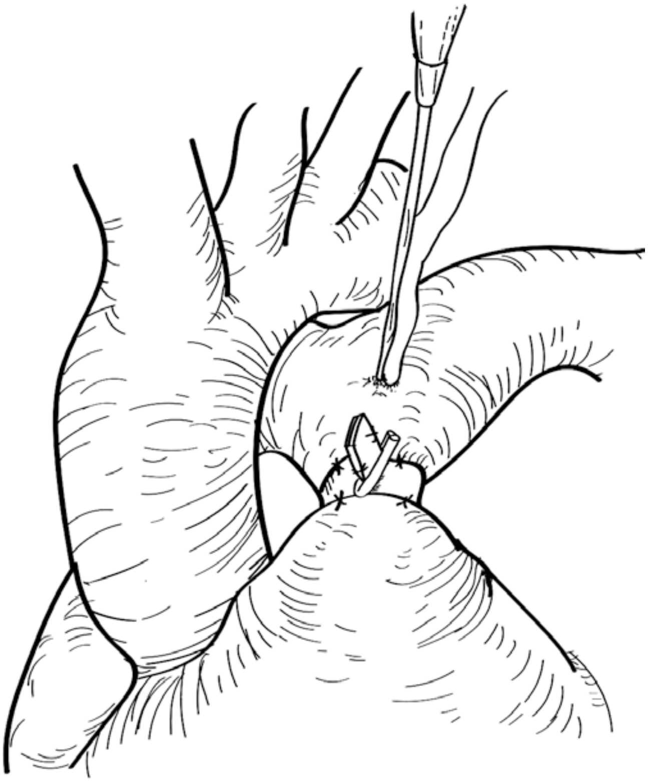

Fig. 89.1 Pulmonary artery banding

The band becomes progressively tighter as the patient grows. However, for left ventricular retraining, proactive serial tightening of the banding may be necessary, either by repeated surgical procedures or, purportedly, by an externally controllable device [8].

Complications

Possible drawbacks of pulmonary banding include distortion of pulmonary arteries and pulmonary and/or atrioventricular valve regurgitation. Furthermore, subaortic obstruction may develop in single ventricle with transposed great arteries prompting a Damus-Kaye-Stansel procedure at subsequent stages.

Banding of Branch Pulmonary Arteries

Bilateral banding can be applied on branch pulmonary arteries directly taking off a major systemic arterial outlet, e.g. in some cases of truncus arteriosus or in those with duct-dependent systemic circulation. Currently, it is mainly used in combination with stenting of patent ductus arteriosus ± balloon atrial septostomy as an alternative to a Norwood procedure for first-stage hypoplastic left heart syndrome palliation in high-risk neonates [9, 10].

Procedures to Increase Pulmonary Blood Flow

Systemic-Pulmonary Shunts

In 1944, Blalock and Taussig introduced the concept of systemic-pulmonary shunt as a means to improve systemic oxygen saturation in cyanotic congenital heart anomalies by increasing pulmonary arterial flow [11]. Since then, several other types of systemic-pulmonary shunt have been devised with peculiar behaviours depending on their systemic source: (1) from aorta or its branches, they act like a patent ductus arteriosus, maintaining a continuous systolic-diastolic arterial flow; (2) from right ventricle, e.g. the right ventricle-pulmonary artery shunt in tetralogy of Fallot/pulmonary atresia or the Sano shunt used in the first-stage palliation of hypoplastic left heart syndrome, producing only a systolic ejection flow; (3) from superior vena cava, as a partial in-series arrangement of the systemic and pulmonary circulations, infusing an additional continuous venous flow into the pulmonary artery.

Indications

Lesions with restricted pulmonary blood flow requiring a systemic-pulmonary shunt procedure include, among others, tetralogy of Fallot with or without pulmonary atresia, single ventricle with tricuspid atresia, pulmonary atresia with intact ventricular septum and Ebstein's anomaly.

Classic Blalock-Taussig Shunt

The classic Blalock-Taussig shunt is the direct end-to-side anastomosis of a transected subclavian artery with the ipsilateral pulmonary artery, performed on the opposite side of aortic arch [11]. Although benefiting from growth potential, it may be afflicted by several potential risks, including: arm ischemia, phrenic nerve injury, distortion of pulmonary artery and technical difficulties during take-down [12, 13].

Modified Blalock-Taussig Shunt

The classic Blalock-Taussig shunt has been progressively replaced by the so-called modified Blalock-Taussig shunt. A vascular graft of proper calibre (see below) is interposed between any brachiocephalic artery branch and the ipsilateral branch pulmonary artery, regardless of the aortic arch side [14]. The graft can be either of expanded polytetrafluoroethylene (ePTFE) or of polyethylene terephthalate (Dacron) [15] and requires ongoing antiplatelet therapy. Since the 1980s, operative mortality and shunt failure rates have been consistently 8% and 6%, respectively. The advantages of this shunt are: (1) high early patency rate; (2) guarantee of adequate length; (3) ease of takedown; (4) preservation of the subclavian artery; and (5) regulation of flow by the size of the artery from which it takes off. The disadvantages include occasional leaking of serous fluid through the interstices of the ePTFE [16] and distortion of the involved pulmonary artery.

The modified Blalock-Taussig shunt can be performed either through a thoracotomy or a median sternotomy. Median sternotomy is preferred for better visualization of structures regardless of the aortic arch side and for proven lower chance of shunt failure [17, 18]. Furthermore, in the case of clinical instability, this approach allows prompt institution of cardiopulmonary bypass. The main, yet manageable, disadvantage is the presence of pericardial adhesions at the time of re-sternotomy [18]. Recommended calibre of the graft is 3.5 mm for babies less than 3.5 kg and 4 mm for infants between 3.5 and 5 kg. After administering 100 IU/kg of heparin, the bevelled proximal end of the graft is end-to-side anastomosed to the chosen brachiocephalic branch (usually the innominate artery). This is followed by an orthogonal end-to-side anastomosis between the distal end of ePTFE graft and the ipsilateral pulmonary artery (Fig. 89.2). In the postoperative period, it is crucial to maintain proper balance between pulmonary and systemic circulations to avoid either diastolic runoff with coronary steal and low cardiac output or low shunt flow with early graft thrombosis [17–19].

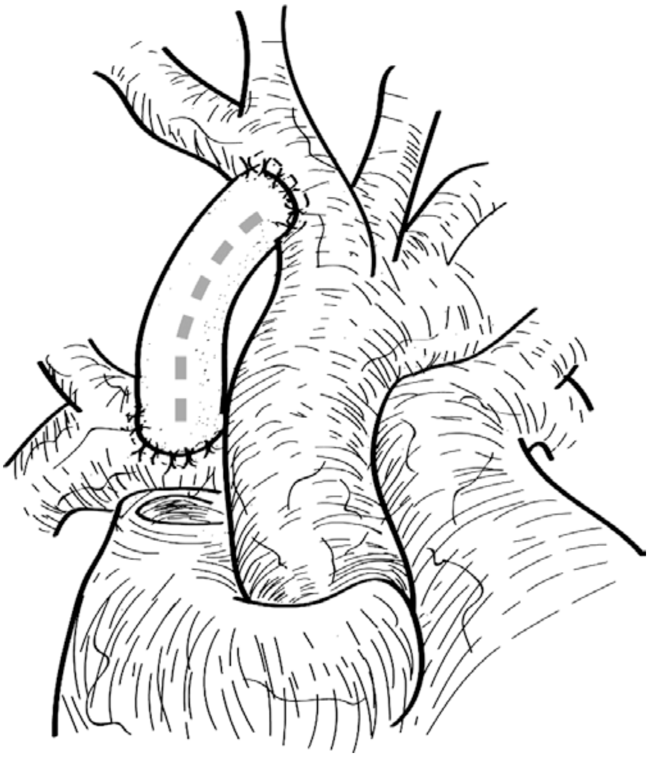

Fig. 89.2 Modified Blalock-Taussig shunt

Potts Shunt

The Potts shunt is an anastomosis between the descending thoracic aorta and the left pulmonary artery, performed through a left thoracotomy [20]. This procedure is no longer adopted as a primary choice because of many complications, e.g. left pulmonary artery aneurysm [21], excessive pulmonary blood flow with resultant pulmonary hypertension, and difficulties in shunt take-down [22].

However, an interesting application of this shunt for suprasystemic pulmonary hypertension, the so-called *reverse Potts shunt*, was reported by Blanc in 2004 [23]. As opposed to blade atrial septostomy characterized by uncontrollable right-to-left intracardiac shunting in the setting of severe pulmonary hypertension, the immediate decrease in right ventricular afterload and the absence of cyanosis of the upper part of the body, obtained by a Potts shunt, may improve symptoms and survival of Eisenmenger syndrome. Noteworthy, the possibility to create a reverse Potts shunt by transcatheter approach has also been recently demonstrated [24, 25].

Waterston Shunt

A Waterston shunt is a surgically created aorto-pulmonary window between the posterior wall of the ascending aorta and the facing segment of the right pulmonary artery, achieved through a right thoracotomy [26]. Progressive distortion of the right pulmonary artery and high incidence of either excessive or insufficient pulmonary blood flow have raised major concerns about this shunt that, in fact, is no longer employed [27].

Central Shunt

A central shunt is an anastomosis between the ascending aorta and the main pulmonary artery, either direct (involving transection of the proximal main pulmonary artery and end-to-side anastomosis with the ascending aorta) or, more frequently, by graft interposition [28, 29] (Fig. 89.3). The advantages of this technique include: (1) no distortion of central pulmonary arteries; (2) growth incentive for small peripheral pulmonary arteries; (3) less chance of shunt blockage; and (4) ease of closure at subsequent repair. The disadvantages are pericardial adhesions at sternal re-entry and unsuitability for patients without confluent pulmonary arteries.

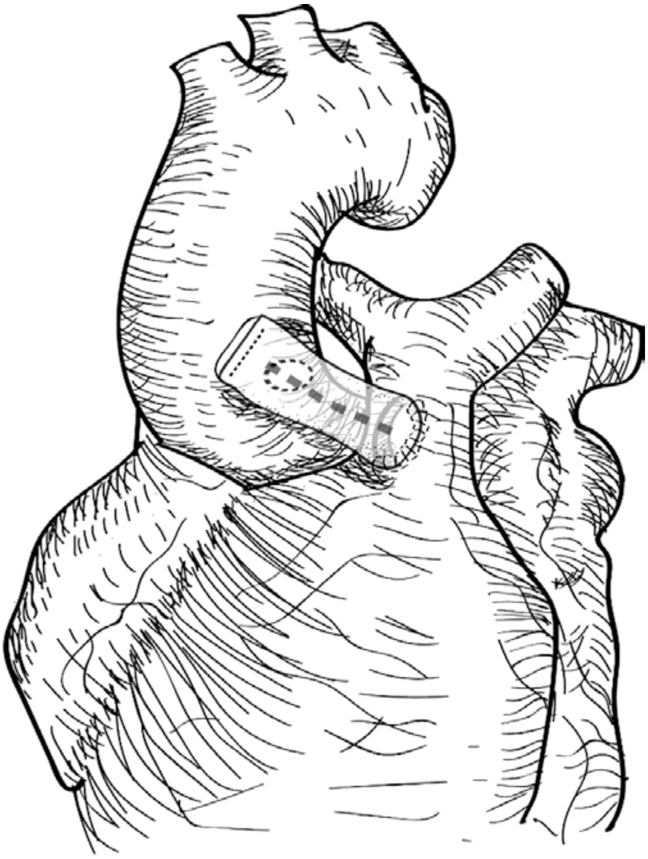

Fig. 89.3 Central shunt

Bidirectional Glenn Shunt

In the bidirectional Glenn shunt, the superior vena cava is end-to-side connected to the right pulmonary artery (Fig. 89.4). As it establishes a partial in-series arrangement of the systemic and pulmonary circulations, it decreases ventricular volume load [30, 31]. Furthermore, by directly providing a quota of highly desaturated systemic venous flow to the lungs, it increases the so-called effective pulmonary blood flow, with the highest capacity of oxygen uptake.

Right Ventricle-to-Pulmonary Artery Shunt (Sano Shunt)

This shunt, producing only a systolic ejection flow, has been extensively used for Norwood stage I procedure as an alternative to modified Blalock-Taussig shunt, to avoid the deleterious effects of diastolic steal [32, 33]. In the setting of hypoplastic left heart syndrome, a Sano shunt assures an increased stability in the immediate postoperative period but raises concerns about the long-term effects of the right ventriculotomy, although of limited extension.

The technique has also been adapted to a wider range of congenital heart lesions, including tetralogy of Fallot with or without pulmonary atresia and others. The main disadvantage of this procedure compared to modified Blalock-Taussig shunt is the mandatory use of cardiopulmonary bypass.

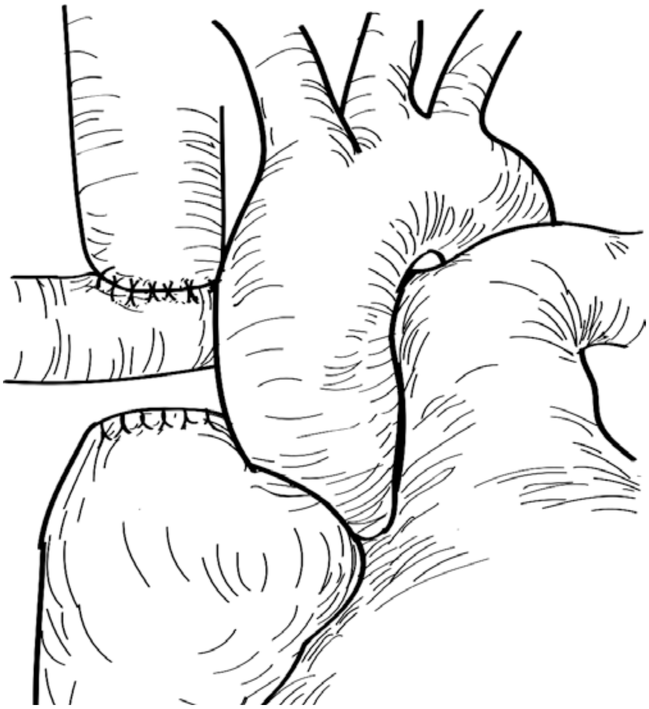

Fig. 89.4 Bidirectional Glenn shunt

Right Ventricular Outflow Tract Stenting

Right ventricular outflow tract stenting improves the pulmonary flow in tetralogy of Fallot while keeping the anterior mediastinum free from adhesions. Quandt et al. reported better growth of distal pulmonary arteries in the patient with tetralogy of Fallot compared to the patient treated by modified Blalock-Taussig shunt [34].

Ductal Stenting

Ductal stenting for neonates and infants with duct-dependent pulmonary circulation has gained a significant role as an alternative to surgical procedures. It carries less risk of severe complications or pulmonary artery distortion and preserves the anterior mediastinum from pericardial adhesions [35].

Procedures to Enhance Mixing

Indications

Biventricular cardiac anomalies with transposition physiology (i.e., with parallel pulmonary and systemic circulations) and single ventricle anomalies with unfavourable streaming may benefit from enlargement of a restrictive atrial communication. This results in enhanced mixing of blood at the atrial level and consequent increase in systemic oxygen saturation.

Balloon Atrial Septostomy

Whenever applicable, the preferred method for an isolated enlargement of atrial communication is a trans-catheter procedure, the so-called balloon atrial septostomy [36]. Whether in the catheter laboratory or at the bedside with transthoracic echocardiographic monitoring, a balloon catheter is advanced through the femoral or umbilical vein into the left atrium and, after inflating the balloon, “forcefully” pulled back into the right atrium, thus disrupting the atrial septum. This procedure is nowadays relatively safe with a success rate of up to 90% (from 50%) [37], but with a number of potential complications like arrhythmias and traumatic or thromboembolic events. Failure of enhanced atrial mixing may depend on a recoiling thick atrial septum (prompting an open atrial septectomy) or on a persistently elevated pulmonary vascular resistance (requiring pulmonary vasodilators).

Blalock-Hanlon Operation

Blalock and Hanlon described a “closed” surgical atrial septectomy in 1950, before the advent of cardiopulmonary bypass [38]. Portions of the right and left atria adjacent to the free wall are occluded by a single C-clamp, together with the right pulmonary veins. Simultaneously, the right pulmonary artery is also occluded to avoid engorgement of the right lung. The right atrium is opened within the clamp and the accessible portion of atrial septum is excised. Thereafter, the clamp is shifted so that the septum drops into the atrial cavity and the atriotomy is closed. This procedure, characterized by acute hemodynamic instability and the risk of paradoxical emboli, is now mostly replaced by open atrial septectomy.

Open Atrial Septectomy

Atrial septectomy is now routinely performed as an independent procedure or as a part of other procedures (e.g. Norwood operation). Cardiopulmonary bypass is instituted, and the right atrium is opened during a period of aortic cross-clamping or induced ventricular fibrillation. The entire tissue within the fossa ovalis is excised, with possible extension into the roof of coronary sinus. Care should be taken to avoid injury to the atrioventricular node or a breach in the wall, especially of the small left atrium.

Palliative Atrial Switch Operation

A palliative atrial switch operation, i.e. Senning or Mustard operation, can be used to mitigate severe cyanosis in patients with transpositions of great arteries, ventricular septal defect and severe pulmonary vascular obstructive disease [39, 40]. The ventricular septal defect in these cases is left open.

Other Miscellaneous Palliative Procedures

Hybrid Palliation

Indications

Hybrid palliation was originally developed as an alternative to Norwood operation for hypoplastic left heart syndrome [9]. The indication has subsequently been extended to all patients with single ventricle physiology and systemic outflow tract obstruction [41]. Conventional Norwood stage I procedure has evolved as the preferred approach in most cases of hypoplastic left heart syndrome. However, the indication is still controversial for the neonate below 2.5 kg, an increased risk factor for Norwood procedure [42, 43]. Infants with hypoplastic left heart syndrome who are planned for heart transplant and those with a borderline-sized left ventricle for possible subsequent biventricular repair may also benefit from hybrid procedure [44].

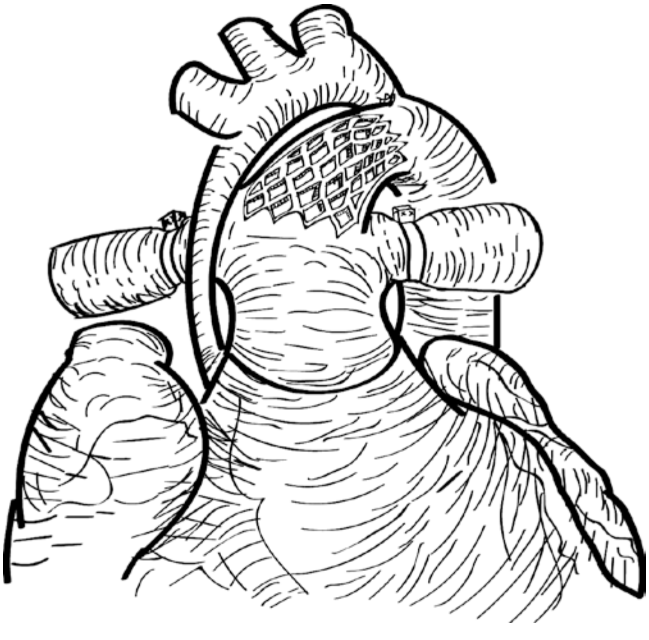

Fig. 89.5 Hybrid palliation

Technique

Hybrid palliation is defined as a combination of transcatheter ductal stenting and surgical bilateral pulmonary artery banding, either in one setting or in sequence. Patency of ductus arteriosus is assured by a self-expanding stent allowing adequate systemic blood flow for both upper and lower body. Pulmonary over-circulation in cardiac conditions with systemic outlet through the main pulmonary artery is controlled by bilateral branch pulmonary artery banding (Fig. 89.5). Balloon atrial septostomy is added according to needs.

Complications

Besides peripheral vascular damage, a hybrid approach is at risk for preferential flow to lower body, neurologic complications, acquired branch pulmonary arteries stenosis and increased complexity of stage II operation.

Conclusion

The aim of palliative operations is to lessen cyanosis, control heart failure or prepare the circulation for later correction when conditions, anatomically as well as physiologically, are suitable for the definitive repair. Although early total correction is now possible in many congenital anomalies, there is still need for palliation when definitive repair is not an immediate option or when single stage correction may carry a significantly higher mortality risk than staged palliation and subsequent correction.

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Coronary Anomalies in Children

90

Phan-Kiet Tran and Victor T. Tsang

High Yield Facts

- Coronary anomalies are rare but potentially lethal conditions.
- Typical anomalies are when the left or right coronary artery arises from the pulmonary artery instead of from the aorta (ALCAPA or ARCAPA), or where the origin is from the aorta but from the wrong aortic sinus (AAOLCA and AAORCA).
- Other anomalies include coronary fistulas and aneurysms.
- The prevalence of anomalous left coronary artery from the pulmonary artery (ALCAPA) is roughly 1 in 300,000 children.
- Only half of the patients with ALCAPA are likely to be diagnosed during infancy.
- Anomalous origin of the right artery from the pulmonary artery (ARCAPA) is extremely rare.
- Once detected, surgical repair should be considered.
- Only a minority of patients may be suitable for conservative approach.
- The aim of surgical repair in ALCAPA and ARCAPA is to prevent pulmonary steal and also achieve antegrade flow.
- Anomalous aortic origin of a coronary artery has a prevalence of 0.1–0.3%.
- Anomalous aortic origin of the right coronary artery (AAORCA) is estimated to be 6 times more common than anomalous aortic origin of the left coronary artery (AAOLCA), and there are a number of anatomic variations.
- Anomalous aortic origin of a coronary artery is the second most common cause of death in children and young adolescent in the United States.
- Surgery is indicated in AAORCA or AAOLCA if the patient has had an ischemic event or if a high risk anatomy is serendipitously discovered in individuals subjected to high level sport activities or physical work load.
- The prevalence of coronary artery fistula in the general population is approximately 0.002% which also represents 14% of coronary artery anomalies.

Introduction

Anomalies of the coronary arteries can cause insufficient flow which leads to heart failure and can in specific setting cause sudden death in the young. Fortunately, anomalies of the coronary arteries are rare. This chapter will focus on coronary issues related to anomalous origin of a coronary artery and coronary fistulas, their anatomy, diagnosis, and treatment (Table 90.1). As for other rare conditions such as Kawasaki disease (Table 90.2) there are a number of excellent reviews [1, 2].

Anomalous Origin of Coronary Arteries

This diagnostic entity carries the most far reaching and lethal consequences for the patients because the anomalies herein are rare and can remain undetected until it may be too late. Here, the left or right coronary artery may originate either from the pulmonary artery, or from the incorrect sinus of the aortic root [3]. Although the anatomy and pathophysiological mechanism may differ, the consequence of these

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Table 90.1 Characteristics of different types of coronary anomalies in children

Coronary departure	Coronary artery affected	Diagnosis	Typical age at presentation	Treatment options	Urgency
Normal	Left	Coronary fistula	Any age	Surgical repair	Depends on symptoms
	Right	Coronary fistula	Any age	Surgical repair	Depends on symptoms
Pulomary origin	Left	ALCAPA	6 months	Surgical repair	Within 24 h
	Right	ARCAPA	Any age	Surgical repair/ Conservative	Depends on symptoms
Aortic origin	Left	AAOLCA	10–12 years	Surgical repair	When stabilised
	Right	AAORCA	Any age	Surgical repair/ Conservative	Depends on symptoms

AAOLCA anomalous aortic origin of left coronary artery, *AAORCA* anomalous aortic origin of right coronary artery, *ALCAPA* anomalous left coronary artery from pulmonary artery, *ARCAPA* anomalous right coronary artery from pulmonary artery

Table 90.2 Overview of Kawasaki disease

Epidemiology
• Considerable differences between different geographical areas, with incidence from 3.4 up to 218.6 cases per 100,000 children less than 5 years
• The incidence of Kawasaki disease (KD) is different according to gender, as males are more prone to develop the disease, with a M:F ratio of 1.4–1.9:1
• Mostly observed in children less than 5 years in over 80% of cases, with a peak incidence in the first 24 months of life
• The incidence of coronary artery aneurysms (CAA) is approximately 15–25% in untreated patients and less than 5% in patients treated with intravenous immunoglobulin (IVIG) within 10 days after the onset of fever
Etiopathogenesis
• The definite etiology of KD is unknown. There is involvement of innate and acquired immunity
Clinical findings[a]
• **Heart**: *coronaritis*, *pericarditis*, *myocarditis*, endocarditis, arrhythmia, mitral regurgitation/aortic and tricuspidal regurgitation (in the acute phase), aortic dilation (in a later phase), cardiac failure, shock
• **Vascular system**: Raynaud's phenomenon, peripheral gangrene
• **Joints**: arthritis or arthralgia
• **Nervous system**: *irritability* (a particularly suggestive symptom of KD, but not yet considered as pathognomonic), *aseptic meningitis*, encephalopathy, seizures, ataxia, sensorineural hearing loss, transient unilateral peripheral facial nerve palsy
• **Gastrointestinal system**: *diarrhea*, *vomiting*, *abdominal pain*, acute abdomen, hepatic enlargement and jaundice, acute acalculous distention of the gallbladder (hydrops), acute pancreatitis, cholestatic jaundice, retropharyngeal abscesses are described in 3.6% of cases
• **Urinary system**: *aseptic pyuria*, proteinuria, urethritis, testicular swelling
• **Skin**: erythema and induration at the site of a previous *bacillus Calmette-Guérin* vaccination
• **Respiratory system**: cough, rhinorrea, slow-resolution pneumonia, pulmonary nodules, and lung infiltrates
Investigations
• Echocardiography remains the instrument of choice to identify CAA during the acute phase of KD up to the first 6 weeks after onset
• Computed tomography or magnetic resonance angiography can be required for an accurate risk stratification via evaluation of the vascular system, especially in growing children
Management
• Acute phase: The initial treatment of KD acute phase includes the combined use of IVIG and aspirin
• Resistant form: Several second-line treatment options are available in the resistant KD, represented by additional IVIG infusions, intravenous methylprednisolone pulses, infliximab, ulinastatin, cyclosporine A, methotrexate, and plasmapheresis
• Surgery: Coronary artery bypass grafting using internal mammary arteries is indicated in:
– Patients with severe occlusive lesions of the left coronary artery
– Patients with severe occlusive lesions in more [2 or 3] vessels
– Patients with severe occlusive lesions in the proximal portion of the left anterior descending coronary artery
– Patients with a compromised collateral circulation
– Patients with previous history of a heart attack (to ensure secondary prevention of heart attacks)
• Heart transplantation: A dozen of KD cases have been reported worldwide for heart transplantation. Heart transplantation is indicated in:
– Patients with significant left ventricular dysfunction
– Patients with potentially lethal arrhythmias
– Patients with significant lesions in the peripheral segments of the coronary arteries

[a] Common features

anomalies is the same: inadequate coronary flow that leads to severe heart failure and death in the case of anomalous pulmonary origin, and sudden death in the case of anomalous aortic origins [4–6]. Increased awareness is the key to correct diagnosis. Indication and timing of surgical repair is still a matter of some controversy. Joint research effort is underway, and hopefully upcoming results from the Congenital Heart Surgeons Society Registry [7] will improve our understanding and management for these patients.

Anomalous Coronary Origin from the Pulmonary Artery

Anomalous left coronary artery from pulmonary artery (ALCAPA) is far more common than anomalous right coronary artery from the pulmonary artery (ARCAPA). The prevalence of ALCAPA is roughly 1 in 300,000 children [8]. But among those with congenital heart defects, the prevalence is 720–1380 in 300,000. The left coronary artery ostium can arise anywhere from the main pulmonary artery or its proximal branches, although most typically from either of the two posterior sinuses of the pulmonary trunk [9] (Fig. 90.1a). The physiological drop in pulmonary resistance and pressure within the first few days after birth leads to insufficient forward flow in the left coronary artery during diastole, and as collaterals develops from the right coronary branches, the flow is reversed from left coronary artery into the pulmonary artery during the entire heart cycle [10]. Although collateral vessels from the right coronary branches may provide some backup supply to the left coronary branches, this is rarely sufficient [11, 12]. Inadequate perfusion of the left ventricular mass is believed to disrupt normal hyperplasia and hypertrophy of the myocytes during the first week of life, which results in a thin walled and markedly dilated left ventricle [13]. A second typical finding is severe mitral regurgitation [14], which is secondary to the left ventricular dilatation and papillary muscle infarction.

Only half of the patients with ALCAPA are likely to be diagnosed during infancy [15]. Unfortunately, symptoms of shortness of breath, poor feeding and weight gain in this age group do not always warrant a chest X-ray which would reveal prominent cardiomegaly. Awareness is therefore important to avoid delayed diagnosis. All children suspected of having myocarditis and heart failure should undergo relevant investigations to rule out the presence of ALCAPA [16]. Cardiac ultrasound will immediately detect a massively enlarged left ventricle and severe mitral insufficiency, and conscious examination should identify a continuous retrograde flow signal from a coronary artery into the pulmonary artery [15]. Computerized tomography (CT) can delineate anatomy [17], and magnetic resonance imaging (MRI) may show extensive myocardial fibrosis [18].

Surgical repair aims to restore normal anatomy to improve and hopefully restore normal diastolic forward flow in the left coronary artery. Depending on the anatomy, different surgical techniques can be used to transfer the left coronary from the pulmonary artery and re-implant it into the aorta. Tension free re-implantation of a left coronary that originates far from the aorta, e.g. on the left lateral aspect of the main pulmonary artery, can be challenging but is doable by extended resection of pulmonary tissue around coronary

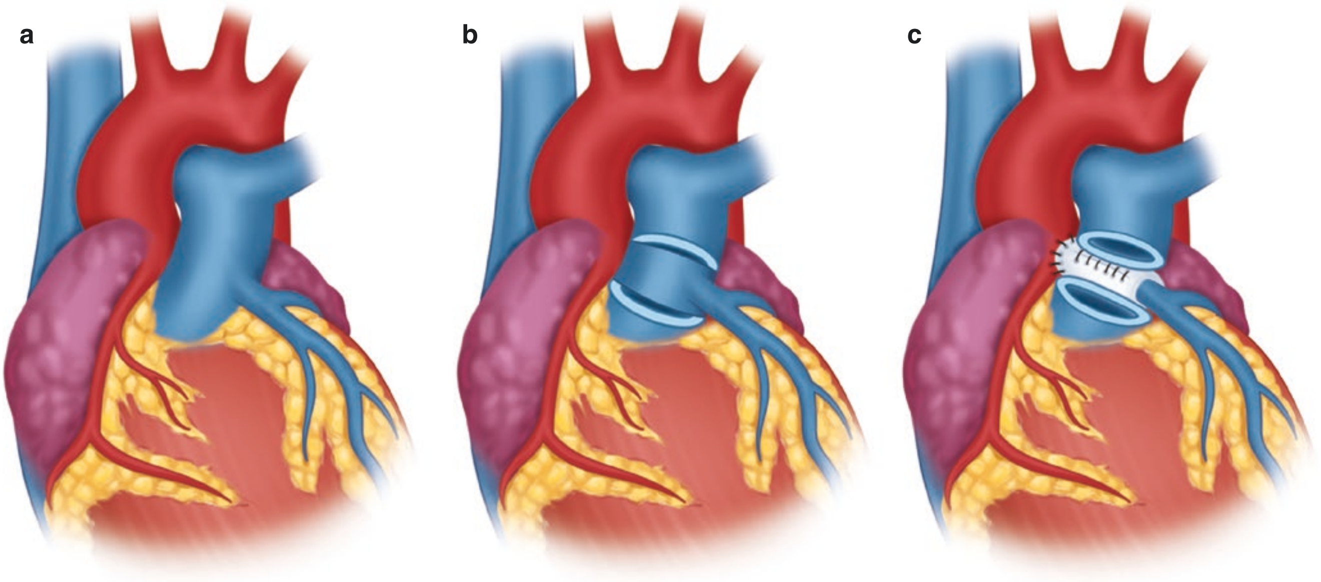

Fig. 90.1 Anomalous left coronary origin from pulmonary artery. (**a**) The most common origins. (**b**, **c**) Surgical technique to create a conduit for reimplantation when the left coronary originates far from the aorta

ostia, which then can be used to tailor a tubular conduit [19] (Fig. 90.1b, c). Remember that ALCAPA is ongoing ischemia. The repair procedure should therefore be scheduled without delays, in spite of the poor left ventricular function. Although not always needed, make sure that postoperative circulatory support, extracorporeal membrane oxygenation (ECMO), is available. Surgery should ideally be performed at congenital heart centers. The normalized perfusion can salvage the remainder of the left ventricular mass and its function, and long-term results are excellent for the majority of patients.

The need of postoperative ECMO varies from none [20], to approximately 5% [21] in different series. Perioperative mortality is generally low [22], although one center has reported a rate as high as 13% [23]. Ten years actuarial survival among 29 patients operated between 1982 and 2000 at Tokyo Women's Medical College was 93% [24]. Hospital for Sick Children in Toronto reported 93% freedom from intervention at 10 years on a series of 47 patients [21]. Fortunately, potential recovery of left ventricular function is high. In the majority of patients where true antegrade coronary flow was achieved, near normal left ventricular volumes were observed by 7–22 months following surgery [13]. Normalization of left ventricular shortening fraction Z score was found at 100 months follow-up [24]. Cardiac MRI is a good, non-invasive and radiation-free investigation in the post-surgical evaluation of ALCAPA repair where important findings such as coronary occlusions and sub-endocardial myocardial fibrosis can be identified [25].

Anomalous origin of the right artery from the pulmonary artery (ARCAPA) is extremely rare. Only 31 cases had been reported in the literature by 2007 [26, 27]. The clinical course is often milder compare to ALCAPA, which may be explained by a different coronary perfusion physiology and the lower myocardial wall tension of the right ventricle [28]. However, a number of patients who died of sudden death have been found to have ARCAPA and myocardial necrosis, which emphasizes the risks of sudden death also in this form of anomaly [27, 28]. Therefore, unless the anomaly is found in older patients, surgical re-implantation into the aorta is a reasonable choice and the most common choice [29]. The aim is to prevent pulmonary steal and hopefully also achieve antegrade flow, and reported results are excellent [29].

Associated cardiac defects such as tetralogy of Fallot [30] and pulmonary valve stenosis [31] have been described, but these combinations are extremely rare.

Anomalous Aortic Origin

In this type of anomaly, the left or right coronary arteries originate from the aorta, but not from the correct sinus. The true prevalence in the general population of this condition is difficult to ascertain. Angiographic studies suggest a figure in the order of 0.1–0.3% [32], which would correspond to 7–21 million cases worldwide. Anomalous aortic origin of the right coronary artery (AAORCA) is estimated to be 6 times more common than anomalous aortic origin of the left coronary artery (AAOLCA), and there are a number of anatomic variations (Fig. 90.2).

Dr. Peter A. Benson was the first to understand the danger of having a left coronary artery that originates from an incorrect sinus of Valsalva [4]. He made the connection between AAOLCA and sudden death based on, at that time, only six reported cases in children and young adults. A more recent study reports that anomalous aortic origin of a coronary artery is the second most common cause of death in children and young adolescent in the United States [33]. The incidence of sudden death because of coronary anomalies are extremely low ranging from 0.00001% to 0.00006% in high risk groups, i.e. those subjected to high physical exertions, such as military recruits [34], marathoners [35], and triathletes [36].

There are a number of anatomical variations as to where and how the coronary artery departs from the aorta. Some coronary arteries come off the aorta in a normal "benign" fashion, but some will run inside the aortic wall, so called an intra-arterial course, and considered as being more "malignant" (Fig. 90.2c–e). In light of the very low incidence of sudden death questions have therefore been raised whether all specific variants carry the same risk. There is a growing consensus on a true risk of sudden death in the setting where the left coronary artery originates from the right coronary sinus (sinus number 2) and runs either intra-mural within the aortic wall or inter-arterial on the outside between the aortic root and the pulmonary trunk (Fig. 90.2c, d). In either case, the mechanism of cardiac ischemia is believed to occur when the coronary artery is squeezed between the two great arteries. The increase of blood flow and volume, particularly in the more distensible pulmonary artery, during exercise can precipitate signs and symptoms of myocardial ischemia.

Unfortunately, this understanding is of little use because the majority of patients remain undiagnosed, and will present with cardiac arrest, usually in conjunction with physical exertion. With adequate resuscitation and immediate transfer to centers with cardiac and mechanical circulatory support capabilities (V-A ECMO), the patient can however be rescued. The patient is typically a child/teenagers between 10 and 14 years old. Diagnosis is confirmed by ultrasound and CT angiography.

Surgery is indicated if the patient has had an ischemic event or if a high risk anatomy is serendipitously discovered in individuals subjected to high level sport activities or physical work load. Corrective surgery can be performed once the left ventricular function has improved in patients who have recovered from an ischemic event. Those with an intra-mural course of the left coronary artery can be corrected by un-

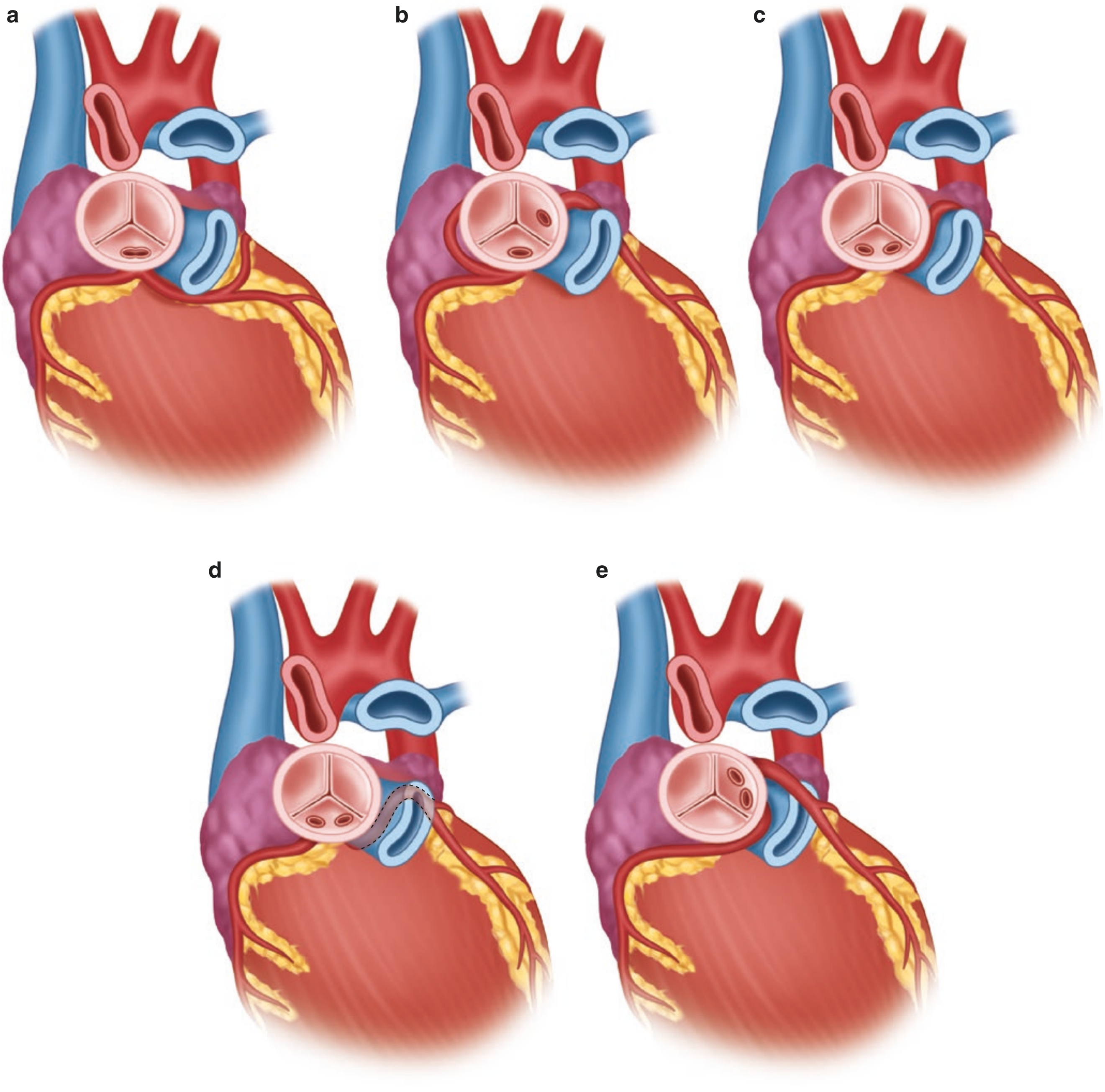

Fig. 90.2 (**a**–**e**) Anomalous aortic origin of coronary arteries. The pathology is considered malignant and associated with high risk of sudden death if left or right coronary artery originates from the wrong sinus, and its course runs between the aorta and the main pulmonary (**c**, **e**) or intra-murally within the conal septum (**d**)

roofing or by incision and opening into the correct sinus followed by enlargement of the new coronary ostia with a patch (Fig. 90.3). Re-implantation of the AAOLCA, into the correct sinus can be done for those with an inter-arterial course. The coronary artery may be smallish and the arterial wall can be very fragile. This is very challenging surgery to do in patients potentially very well and asymptomatic at rest. Another approach would involve the shifting of the pulmonary bifurcation to the left pulmonary artery to create 'space' for the inter-arterial course negating any exertional compression from the PA [37]. The surgical approaches have been extensively reviewed [38].

Early results of surgery are excellent. Two recent series of 50 and 53 patients reported 100% survival [39, 40]. Some degree of chronotropic impairment but normal physical tolerance has been reported [41]. Return to competitive sport is still a matter of controversy, but could be considered if the patient has undergone careful assessments with exercise test-

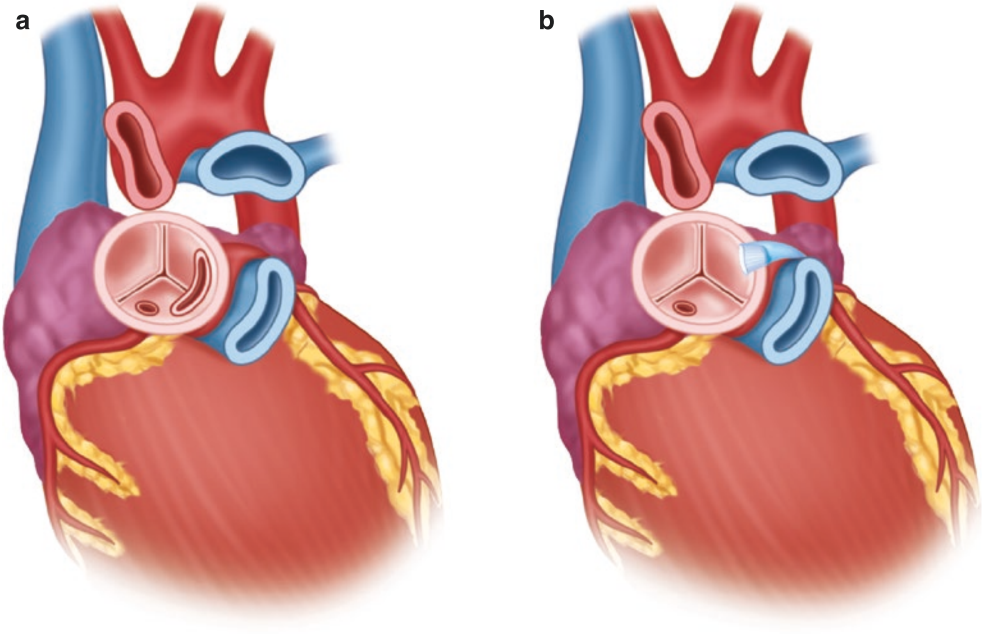

Fig. 90.3 Surgical repair of AAOLCA. (**a**) Unroofing. (**b**) Incision into the correct aortic sinus and patch augmentation with autologous pericardium

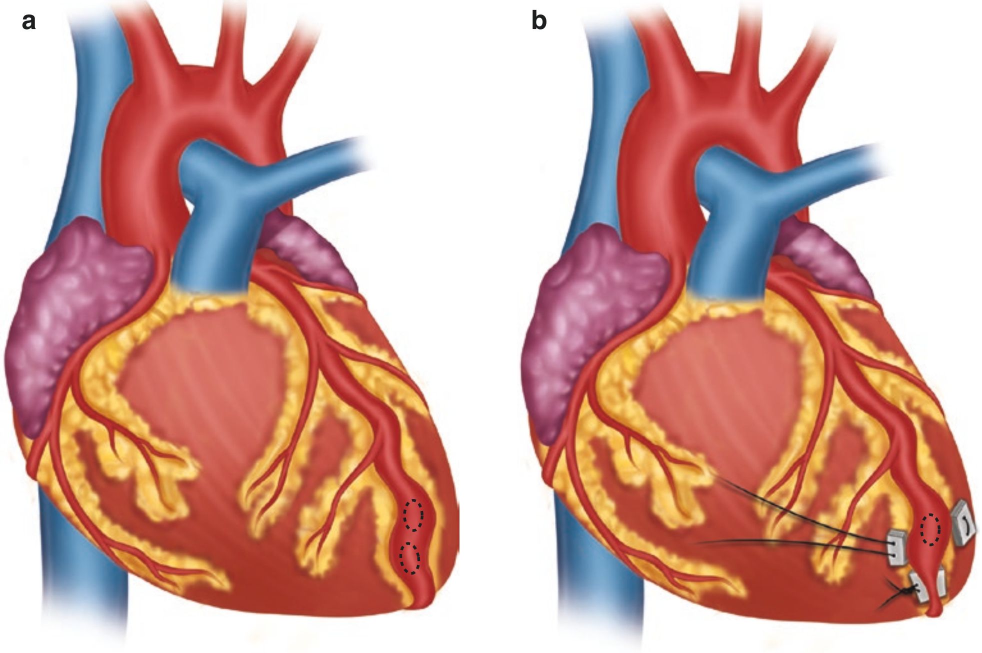

Fig. 90.4 (**a**) Coronary fistulas from at the distal end of the left anterior descending artery entering the apical portion of the left ventricle. (**b**) The fistulas are closed with pledgeted sutures

ing and imaging investigations [42]. Ostial stenosis of the re-implanted coronary artery is a potential concern and this would require long term follow up,

Coronary Artery Fistula

The prevalence of coronary artery fistula in the general population is approximately 0.002% which also represents 14% of coronary artery anomalies. The fistula can arise from either the right or left coronary artery and drains in one or several locations of the heart, including the right ventricle, left ventricle, right atrium, and pulmonary artery [43] (Fig. 90.4). It can become aneurysmal and the external appearance can be alarming (Fig. 90.5). The majority of the patients are likely to have multiple fistulas, and the majority will also have associated heart defects including mitral regurgitation, tricuspid regurgitation, aortic stenosis, or double outlet right ventricle [44].

The fistula causes a steal phenomenon that causes myocardial ischemia and volume overload to the ventricular

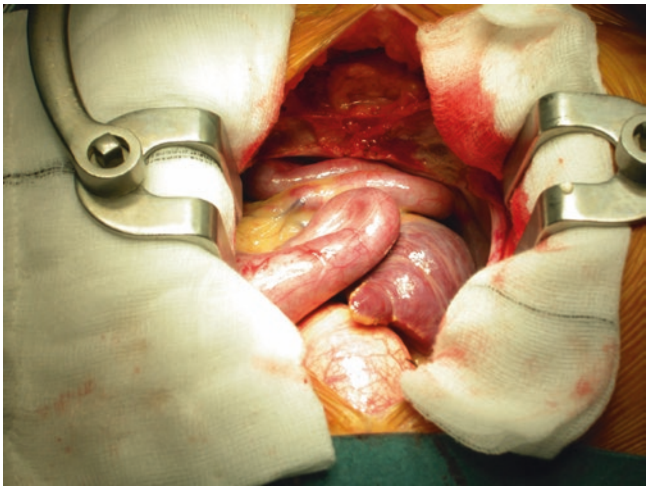

Fig. 90.5 Right coronary fistula can become aneurysmal and the external appearance can be alarming

chamber at the receiving end. Patients present with angina, and symptoms of heart failure. Cardiac ultrasound with color Doppler is highly sensitive for the detection of fistulas, but coronary angiography with measurement of oxygen saturation remains the gold standard. The origin of the important coronary branches such as the posterior descending artery is important at time of surgery.

Clinical symptoms of heart failure and/or angina warrant fistula closure. The majority of cases with isolated connection can be managed with catheterization techniques where coils or umbrellas can be deployed. For multiple fistula connections with aneurysmal formation of the right coronary artery (Fig. 90.5), surgical closure is performed and coronary artery bypass grafting is required for the posterior descending artery. Different surgical techniques can be employed (Fig. 90.4). Surgical results are excellent. Several groups have reported no mortality in their series [45, 46].

Fistulas are of particular importance in the setting of pulmonary atresia and intact ventricular septum because the coronary blood flow may be dependent on the enclosed hypertensive ventricle, and where decompression may lead to death [47].

Conclusion

Congenital abnormalities of the coronary arteries are extremely variable and include anomalies of their origin (atresia, anomalies of origin from the aorta or from the pulmonary artery), the course of the epicardiac coronary branches (intramural, myocardial bridge) and distal connections (coronary-cardiac chamber fistulae). High-risk anomalous coronary anatomy in the appropriate clinical setting can require surgical intervention with decisions including correction via reimplantation of a coronary artery, alteration of the anomalous coronary artery course without reimplantation, or bypass of an anomalous coronary artery. Given the rarity of coronary anomalies, there is limited data in the literature, and significant controversy related to the management issues. The management of coronary anomalies requires comprehensive clinical history, thorough assessment of cardiac function, and detailed anatomic imaging. Future studies will need to address the long-term outcome based on detailed assessment of original anatomy and surgical approach.

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Congenital Valvar and Supravalvar Aortic Stenosis

91

Viktor Hraska and Joseph R. Block

High Yield Facts

- Valvar aortic stenosis is the most common type of left ventricular outflow tract obstruction.
- Congenital aortic valve disease ranges from newborn critical aortic stenosis and shock to teenage asymptomatic aortic stenosis and progressive ventricular dilatation.
- Echocardiography provides essential information about the aortic valve and left ventricle.
- Both balloon and open interventions are established and effective treatments for newborns with critical aortic stenosis.
- Repair in older children with aortic stenosis can restore function and maintain growth potential, however is associated with limited durability.
- Replacement of aortic valve can be autologous (Ross procedure), mechanical, or bioprosthetic.
- Younger patient's requiring replacement can be excellent candidates for the Ross procedure.
- The supported Ross procedure may offer excellent long term durability in the older age group.
- In some children the best alternative is still to use a prosthetic valve, despite the well-known drawbacks of this procedure.
- Limited durability of bioprosthetic valves and aortic homografts render them secondary replacement options for most children.
- Any valve replacement in children is palliation and re-interventions are unavoidable.
- Congenital supravalvar aortic stenosis is the least common form of left ventricular outflow tract obstruction.
- Congenital supravalvar aortic stenosis results from haploinsufficiency of the elastin gene on chromosome 7q11.23.
- Microdeletion of elastin gene results in Williams-Beuren syndrome, which manifests as an elastin arteriopathy in addition to several other features including intellectual disability, hypercalcemia, and facial abnormalities.
- Patients with non-syndromic supravalvar aortic stenosis have a similar arteriopathy as patients with Williams-Beuren syndrome, but typically have normal intelligence and lack dysmorphic features.
- Sudden death has been well-reported in patients with supravalvar aortic stenosis and is believed to be precipitated by acute coronary ischemia.
- Echocardiography and magnetic resonance imaging provide essential information about the degree of anatomic narrowing in the ascending aorta, as well as evaluate for stenosis is other parts of the arterial or pulmonary tree.
- Surgery is the only effective way of treatment with the goal to achieve a symmetric enlargement of the aortic root and other narrowed segments of the aorta and head vessels.

Congenital Aortic Valve Stenosis

Introduction

Valvar aortic stenosis is the most common type of left ventricular outflow tract obstruction. In the pediatric population, a congenitally malformed aortic valve, i.e. bicuspid aortic valve, is by far the most common cause of aortic stenosis.

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A bicuspid aortic valve has an estimated prevalence in the general population of between 0.5% and 2%, making it the most common congenital heart defect [1]. Bicuspid aortic valve is often associated with other congenital heart defects, most commonly with ventricular septal defect and other left-sided obstructive lesions such as coarctation of the aorta [2].

Anatomy

Stenosis is the result of deficiency in, or absence of, one or more commissures, leading to a unicuspid, bicuspid or tricuspid valve with fused commissures. This is often accompanied by myxomatous changes and thickening of the valve cusps, with or without commissural fusion, and hypoplasia of the valvar annulus [3].

In older children, most frequently seen (in about 70% of cases) is a bicuspid valve with the two commissures arranged as anterior and posterior, although it can also present with a horizontal opening. There may be a third partially fused or false commissure (raphe). There are usually variable degrees of peripheral fusion of one or both commissures creating a stenosis (Fig. 91.1). If the free edges of both thickened bicuspid cusps are taut with no extra length and equal in length to the diameter of the aortic root, they cannot open completely and thereby produce obstruction. Abnormal tricuspid aortic valves may not be obstructive during early infancy, but may become stenotic later in life due to cusp thickening and calcification.

Pathophysiology

Valvar aortic stenosis physiologically results in increased wall stress, or afterload, on the left ventricle. Chronic increase in left ventricular afterload from hemodynamically significant aortic stenosis, triggers compensatory structural changes characterized by concentric remodeling and hypertrophy of the left ventricle [4].

Progressive hypertrophy also results in an imbalance between coronary supply and myocardial demands. This imbalance results in microvascular and subendocardial ischemia that further contribute to myocardial fibrosis and myocardial dysfunction. Subendocardial ischemia may be exacerbated by a short diastolic coronary filling period that results from prolonged systolic ejection across a stenotic aortic valve, as well as from the tachycardia during periods of exercise. As the degree of aortic stenosis progresses and becomes severe, and not relieved by intervention, the compensatory mechanisms may fail. The wall thickness does not increase in proportion to the left ventricular systolic pressure. The increased wall stress and afterload results in progressive left ventricular chamber dilatation with concomitant increase in end-diastolic volume and pressure, and eventually decreased contractility [5].

Clinical Features

The clinical presentation of aortic stenosis is variable and in the neonate or young infant can be one of three ways. Newborns with "critical" aortic stenosis present with symptoms consistent with cardiogenic shock following closure of the arterial duct. The second mode of presentation is seen in neonates or young infants with left-sided cardiac failure, but without dependency on the arterial duct to maintain systemic perfusion. In the third situation, patients may be referred for evaluation of a systolic murmur, but are otherwise asymptomatic without signs of congestive cardiac failure.

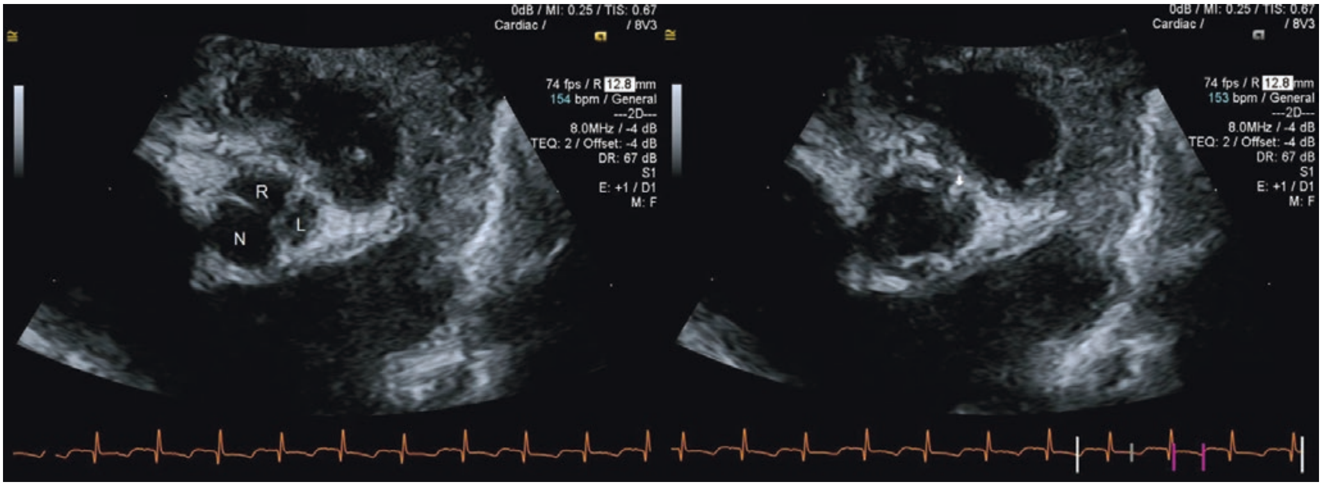

Fig. 91.1 Parasternal short axis view by transthoracic echocardiogram demonstrating a bicuspid aortic valve with fusion between the right and left coronary cusps. *R* right coronary cusp, *L* left coronary cusp, *N* noncoronary cusp, *Arrow* fusion point between right and left coronary cusps

Older children, outside of the infancy period, are typically asymptomatic. Patients with moderate or severe aortic stenosis may present with complaints such as fatigue, exertional dyspnea, chest pain, and syncope. These symptoms results from the inability of the left ventricle to increase its output appropriately with exercise warrant urgent evaluation.

Diagnosis

Electrocardiogram

The electrocardiogram is usually normal but in severe valvar aortic stenosis there may be evidence of left ventricular hypertrophy with or without left ventricular strain.

Chest Radiograph

Chest radiography is typically unremarkable. In neonates with critical aortic stenosis there may be cardiomegaly with pulmonary venous congestion. A dilated ascending aorta may be visible.

Echocardiogram

Both two-dimensional and three-dimensional echocardiography usually provide complete diagnostic and hemodynamic information. In determining actual valve morphology, it is important to determine cusp thickness, size, mobility, annular diameter at hinge points, and the height difference between cusp margin and aortic insertion in the long-axis view. Native commissural function can also be determined by these non-invasive means. Anatomic factors such as leaflet height can be important determinants of valve function and are important details when considering valve repair [6]. The Doppler peak instantaneous gradient across the stenotic aortic valve can be greatly underestimated in a situation of low cardiac output with depressed left ventricle contractility and right-to-left shunt at ductal level. However, in patients with normal ventricular function, the severity of aortic stenosis is graded according to well-established peak Doppler gradient measurements as mild (<40 mmHg), moderate (<60 mmHg) and severe (>60 mmHg) [7]. These are usually an overestimate of the measured peak to peak gradients in the catheterization laboratory, even when measured concurrently, given the variation in timing of each peak in the peak systolic ejection gradient. Mean aortic valve gradients are a better surrogate for the peak to peak catheterization gradient [8], as these were the original indications for outcomes and the need for intervention (Table 91.1). In addition, a thorough evaluation for associated cardiac defects is necessary and can impact both timing and type of intervention. Due to risk for progressive dilation of the ascending aorta these dimensions should be monitored and compared to age-matched controls.

Table 91.1 Recommendations of grading of aortic stenosis severity

Aortic stenosis severity	Jet velocity (m/s)	Mean pressure gradient (mmHg)
Mild	2.0–2.9	<20
Moderate	3.0–3.9	20–39
Severe	>4.0	>40

Adapted from Nishimura et al. [8]
m/s meters per second

Cardiac Magnetic Resonance

Cardiac magnetic resonance provides precise information on left ventricular size, ventricular function, ejection fraction, and regional wall dysfunction. This modality can also provide reliable information about valvar dysfunction including accurate quantification of aortic regurgitation. Further, magnetic resonance imaging provides the ability to assess for myocardial fibrosis and calculate ventricular mass. At this point, two-dimensional and three-dimensional echocardiography are superior in their ability to assess aortic valve morphology and to calculate pressure gradients. Further, obtaining a cardiac magnetic resonance study of infants and young children will require general anesthesia, which further limits its applicability.

Cardiopulmonary Exercise Testing

In those patients with mild to moderate stenosis, exercise stress testing could be helpful in eliciting symptoms or objective measures of ischemia, repolarization abnormalities, arrhythmias or exertional hypotension that may not be evident from routine history or evaluation. Exercise testing may be considered in asymptomatic patients to ensure that they can tolerate desired physical activities with the absence of symptoms, exercise-induced hypotension, or ischemia [9]. Symptomatic patients with severe aortic stenosis should avoid testing.

Cardiac Catheterization

With the advancement of non-invasive imaging, cardiac catheterization is used primarily for intervention rather than for diagnosis. However, it can be used selectively for invasive hemodynamic measurements when noninvasive tests are inconclusive or when there is a discrepancy between noninvasive tests and clinical findings regarding the severity of aortic stenosis.

Management of Critical Aortic Stenosis

Medical Management

Critically ill neonates are stabilized by aggressive resuscitation, while patency of the arterial duct is maintained by prostaglandin E1 infusion. A trial discontinuation of prostaglandins should be undertaken and dependency is an indication for neonatal intervention. If ductal closure is tolerated, intervention (balloon valvuloplasty or open valvotomy) is indicated on a semi-elective basis. Additional medical management, such as inotropic medications and diuretics, may be indicated prior to intervention in young infants with additional symptoms.

Timing of Intervention

In the neonate with critical aortic stenosis and ductal-dependent systemic circulation, there may be varying degrees of hypoplasia of the left ventricle and other left-heart structures. Various predictive formulas [9–11] have been proposed and are often calculated, but there is no consensus on what is definitively required to establish a successful biventricular correction [11].

A reduced dimension of the mitral valve orifice is a well-recognized risk factor for death [12]. Therefore, if the mitral valve annulus diameter is <7 mm in a neonate, if there is an indexed Z score of <−2, or if there is severe inflow obstruction, caregivers often consider single-ventricle palliation with some attempting to promote left ventricular inflow with atrial septal defect restriction and endocardial fibroelastosis resection, if the remainder of the left ventricle is well developed or surgically reparable.

Hypoplasia of the aortic annulus (<5 mm), ratio of left and right ventricular lengths <0.8, a cardiac apex not formed by the left ventricle and the presence of endocardial fibroelastosis may also be relative contraindications for simple open valvotomy or balloon valvuloplasty [9, 11].

Predominantly retrograde flow in the ascending aorta is suggestive of severely hypoplastic or stenotic left heart structures and most often a single-ventricle palliation will be necessary; however, the presence of total or predominant antegrade blood flow in the ascending aorta and transverse aortic arch correlates with survival after a biventricular type of repair [7].

Generally, for biventricular aortic valve stenosis candidates, the treatment choice is between balloon valvuloplasty and open valvotomy. At worst, particularly if the left heart structures are small or if there is substantial mitral valve involvement, a uni-ventricular pathway may need to be considered. In borderline situations, the hybrid univentricular approach might help to select the proper treatment plan later on.

Surgical Intervention

Open valvotomy [12–15] allows construction of a cusp anatomy that is as close as possible to the normal anatomy. Shaving of thickened cusps, excision of obstructive myxomatous nodularities and mobilization of the cusps effectively increase the orifice area of the valve in any type of morphology, with a minimal risk of creating regurgitation. If commissural posts are developed, tricuspidization of valve is usually possible, thus preserving the native aortic valve in the majority of patients in the long run. Surgical intervention also has the advantage of addressing associated cardiac lesions at the same time.

Currently early mortality is reported to be 3–9% [12, 14, 15]. Overall survival is between 70% and 90% at 1 year and usually remains unchanged at 5 years and 10 years of follow-up. The 10 year event-free survival for critical neonates is from 50% to 70% [12–14]. These figures compare favorably with the 29–54% event-free survival at 10 years reported after balloon valvotomy [13, 14, 16].

Catheter Intervention

At many centers, transcatheter balloon aortic valvolplasty is considered first-line treatment for critical aortic valve stenosis. Ballooning relieves aortic stenosis by causing a rupture along the lines of least resistance, either along the underdeveloped commissures or into the cusp tissue.

Early mortality in critical aortic stenosis after balloon valvuloplasty is from 4% to 10% [16–19]. The IMPACT multicenter collaborative study [18] reported on acute outcomes after balloon dilation in a large cohort of patients with critical aortic stenosis. They noted 63% had an optimal or adequate outcome (gradient ≤35 mmHg and aortic regurgitation increased by ≤1 grade, or no increase in aortic regurgitation in those with preexisting aortic regurgitation) while 37% did not meet these criteria and were defined as having inadequate outcomes (17% due to an increase in aortic regurgitation, 13% to a combination of aortic stenosis/aortic regurgitation and about 7% to a residual gradient >35 mmHg). The large multicenter registries [18, 19] have demonstrated that about 16–20% of all patients and 30–40% of neonates had some sort of procedural complication.

Hybrid Approach

A hybrid procedure that incorporates both catheter and surgical modalities serves as a bridge to a more definitive repair for patients with a borderline left ventricle and/or depressed left ventricular function [12, 20, 21]. A hybrid approach may involve some combination of bilateral pulmonary banding, enlargement of the atrial septal communication to decompress the left-heart, maintaining patency of the arterial duct, and either a balloon or open valvotomy [22]. This concept may significantly reduce the risk of a definitive procedure by providing patients more time to recover, mature and 'declare themselves' as either one- or two-ventricle candidates [21].

Long-Term Outcomes

Both balloon valvuloplasty and open valvotomy are firmly established as effective initial treatments, with encouraging survival benefits [12–16, 18, 19, 23]. Mortality is associated with hypoplasia of the left heart structures and the presence of endocardial fibroelastosis [24]. Both methods, however, are palliative procedures and reintervention is likely. Whereas patients undergoing open valvotomy are more likely to have residual stenosis, those undergoing balloon valvotomy are more likely to develop progressive insufficiency. Tricuspid valve morphology showed superior long term outcomes of open valvotomy in comparison with balloon valvuloplasty regarding preservation of the native aortic valve [3, 12].

Management of Non-critical Aortic Stenosis

Medical Management

There are no medical therapies that are proven to prevent or delay the progression of stenosis or need for intervention in the asymptomatic patient. Treatment of hypertension, if present, is reasonable to reduce the overall afterload on the left ventricle, however, medications for afterload reduction are not indicated in normotensive patients.

Due to risk for sudden death with exercise, activity restrictions should be considered in patients with severe aortic stenosis. The American Heart Association and American College of Cardiology currently recommend that patients with severe aortic stenosis be restricted from competitive athletics, and only participate in low-intensity activities. Those with mild or moderate aortic stenosis can participate in all competitive sports as long as they have no symptoms with exercise, ≤mild left ventricular hypertrophy, absence of left ventricular strain pattern on electrocardiogram, and normal maximum exercise stress test without evidence of ischemia, arrhythmias, or drop in blood pressure [25].

Although patients with bicuspid aortic valve are at risk for endocarditis, antibiotic prophylaxis is not recommended prior to dental work or other procedures [8, 26]. However, patients should be counselled on the importance of good oral and skin hygiene to reduce the risk of bacteremia from daily activities.

Timing of Intervention

The timing for aortic valve intervention is not as clearly defined in the setting of an asymptomatic pediatric patients with severe aortic valve stenosis (Table 91.2). Timing is based on weighing the relative risks of no-intervention (i.e. risk of congestive heart failure and sudden death) vs. the risks associated with the procedure (catheter or surgical).

Table 91.2 Indications for intervention for severe valvar aortic stenosis

- Left ventricular systolic dysfunction
- Symptoms of heart failure, syncope, exertional dyspnea, or angina
- Asymptomatic with mean Doppler-derived gradient >60 mmHg by echocardiography
- Asymptomatic with progressively reduced exercise capacity on cardiopulmonary exercise testing
- Asymptomatic with high-risk exercise stress test demonstrating symptoms of angina, ischemic electrocardiographic changes, or hypotension during exertion

In adults with severe aortic stenosis, the guidelines published by the American College of Cardiology and American Heart Association recommend aortic valve intervention if there is associated (1) left ventricular systolic dysfunction, defined as ejection fraction <50%, and/or (2) symptoms of heart failure, syncope, exertional dyspnea, angina, or presyncope by history or on exercise testing [8]. Children and young adults, however, are generally lower surgical risk than adult patients. Also, with a longer life-expectancy, there may be advantage in earlier intervention to preserve left ventricular systolic function before irreversible maladaptive myocardial remodeling occurs. This may justify earlier intervention in children with severe aortic valve stenosis even prior to the onset of symptoms or ventricular dysfunction. A mean pressure gradient ≥60 mmHg across the aortic valve by echocardiography has been recommended as an indication for intervention in asymptomatic young patients [8].

Timing may also be supported with the use of exercise stress testing to determine need for early intervention in asymptomatic children with severe aortic stenosis and preserved left ventricular systolic function by demonstrating decrease in exercise capacity, eliciting exertional symptoms, measuring a fall in blood pressure with exercise, or demonstration of ischemic or repolarization changes on electrocardiogram during exercise. These high risk clinical features would indicate need for aortic valve intervention.

Catheter Intervention

Transcatheter balloon aortic valvuloplasty is similar to that for neonates. Balloon valvuloplasty may be considered in young adults with congenital aortic stenosis. This is typically not successful in older adults due to significant calcification of the cusps and suboptimal results.

When compared with open valvotomy, the advantages of balloon aortic valvuloplasty include avoidance of cardiopulmonary bypass and sternotomy, shorter hospital stay, and lower costs. Long-term survival is similar in both groups with a 10-year survival of 90% in surgical group versus 87% in the balloon group [27]. The risk for aortic valve regurgitation is higher after balloon intervention relative to surgery. Freedom from moderate to severe aortic regurgitation is about 60% at 10 years [16]. In a comparative meta-analysis, the 10-year freedom from re-intervention was lower following balloon intervention at 46% compared with 73% following surgical intervention [27]. However, the freedom from aortic valve replacement was similar between both groups. Another single-center study also reported lower freedom from re-intervention of 27% after balloon valvuloplasty versus 65% after open valvotomy at 5 years of follow-up, as well as a higher need for aortic valve replacement in the balloon group [14].

Surgical Intervention

Open valvotomy for non-critical stenosis can be performed with very low mortality (2–3%). Bicuspidization of unicuspid valve in young adult works well [28]. Conversion of congenitally bicuspid aortic valves to tricuspid arrangement might confer better outcomes, probably due to reduction in cusps stress load and improved flow patterns, by providing optimal effective orifice area. Reconstruction is safe, with early mortality approaching zero and with 5-year freedom from valve replacement up to75% [29]. In general, early valve function after reconstruction is excellent, however long term durability of repair is unknown [30].

In patients where aortic valve repair is not feasible, valve replacement is performed. Options for aortic valve replacement include (1) mechanical prosthetic valve, (2) Ross or pulmonary autograft procedure, and (3) bioprosthetic valve. Any aortic valve substitute in children has certain drawbacks. Bioprosthetic aortic valve replacement options are typically not utilized in pediatric patients and young adults due to rapid degeneration and limited durability. Mechanical valve replacement in children is complicated by the need for systemic anticoagulation, by lack of annular growth and by patient-prosthesis mismatch. On the other hand, mechanical aortic valve replacement might be a life-long solution, mainly for patients where large sizes (≥21 mm) of the valve can be inserted.

The Ross procedure is an attractive alternative to a mechanical prosthesis, but is not a cure for aortic valve disease. The advantages of the Ross procedure are the superior hemodynamic performance, the growth potential, the low endocarditis risk, low thrombogenicity and the lack of need for anticoagulant therapy [31, 32]. The main drawbacks of Ross procedure include concern for progressive neo-aortic root dilation, neo-aortic valve regurgitation, and need for reoperation to address pulmonary homograft dysfunction [33–35]. In older patients technique of supported Ross is preferable to avoid dilatation of neoaortic root [36].

Durability limitations of the Ross procedure become apparent by the end of the first postoperative decade, in particular in younger patients [37]. The rate of autograft deterioration and the right ventricular outflow tract deterioration are estimated at 1.69%/patient-year and 1.66%/patient-year respectively in a mixed pediatric population [33]. Overall, the risk of re-operation is approximately 10% at 10 years, either on the autograft or the right ventricular conduit [38]. In young adult patients, the overall survival and freedom from reintervention was not significantly different following the Ross procedure compared with mechanical valve replacement at mean follow-up of 14 years [39].

Long-Term Outcomes

Life-long follow up is required for patients with congenital valvar aortic stenosis, both before and after intervention. Aortic valve intervention, whether it consists of balloon valvuloplasty or surgical repair/replacement, should be considered palliative, and subsequent monitoring is required to evaluate for need for re-intervention overtime. Ascending aorta dimensions also requires monitoring for patients with bicuspid aortic valve, due to the risk for progressive aortic dilation and dissection.

Supravalvar Aortic Stenosis

Introduction

Congenital supravalvar aortic stenosis is the least common form of left ventricular outflow tract obstruction, with an estimated incidence of 1 in 20,000 live births [40]. It represents one manifestation of a diffuse arteriopathy characterized by thickening of the media or intima layers of the ascending aorta, as well as other systemic and pulmonary arteries.

Congenital supravalvar aortic stenosis results from haploinsufficiency of the elastin (ELN) gene on chromosome 7q11.23. Disruption of the ELN gene results in reduced and disorganized elastin fibers in the arterial media, along with increased number of hypertrophied smooth muscle cells and increased collagen deposition [41].

Traditionally, supravalvar aortic stenosis has been associated with Williams-Beuren syndrome. This results from a microdeletion of ELN gene, which manifests as an elastin arteriopathy and has other features including intellectual disability, hypercalcemia, and facial abnormalities. Point mutations in the ELN gene result in non-syndromic or familial forms of supravalvar aortic stenosis. These patients have a similar arteriopathy as patients with Williams-Beuren syndrome, but typically lack the other associated features [42].

Anatomy

Most commonly, supravalvar aortic stenosis presents as a discrete, “hour-glass”-like narrowing of the ascending aorta near the sino-tubular junction (Fig. 91.2). However, in about 25–30% of cases there is more diffuse narrowing of the ascending aorta that may extend into the aortic arch.

Histology demonstrates reduced and disorganized elastin fibers in the arterial media, along with increased number of hypertrophied smooth muscle cells and increased collagen deposition. Other arteries with high elastin fiber content can

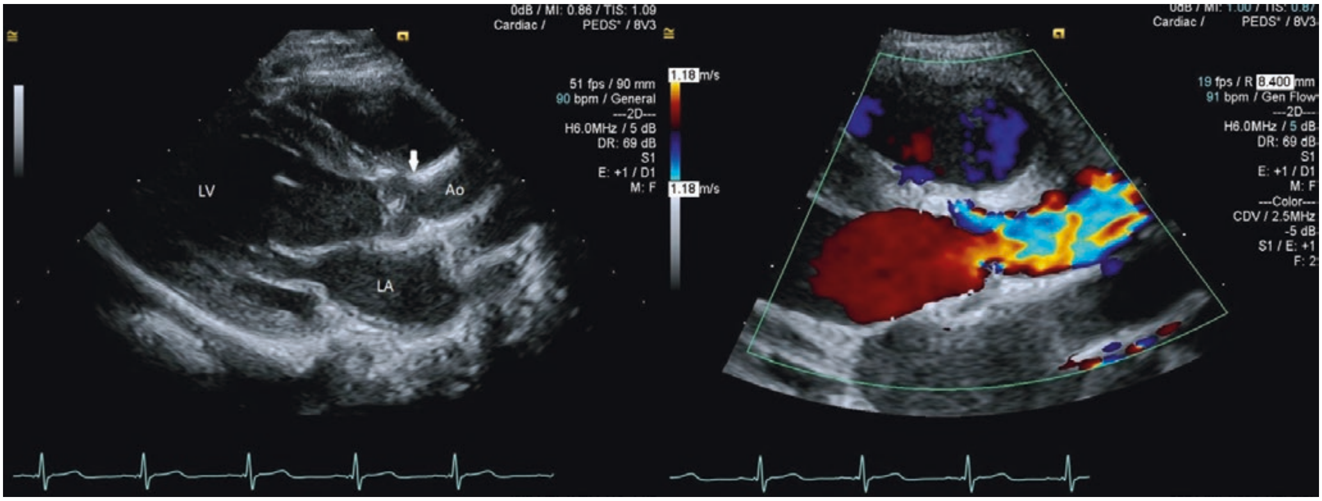

Fig. 91.2 Transthoracic echocardiogram image in the parasternal long axis that demonstrates supravalvar aortic stenosis. Narrowing is noted at the sinotubular junction. Note the color Doppler turbulence starts in the supravalvar region. *LV* left ventricle, *LA* left atrium, *Ao* aorta, *Arrow* supravalar narrowing

also be affected, including progressive stenosis of the proximal descending aorta, as well as pulmonary, coronary, mesenteric and renal arteries. Aortic and mitral valve abnormalities have also been reported [43].

Pathophysiology

Stenosis of the ascending aorta results in increased afterload to the left ventricle, resulting in compensatory left ventricular hypertrophy, similar to the remodeling changes seen with valvar aortic stenosis. However, in addition the coronary arteries are also subject to high pressure and coronary insufficiency is a concerning complication in this setting. This may result from a combination of thickening of the coronary ostia, thickening of the aortic wall above the coronary ostia, premature atherosclerosis, or adhesion of the aortic valve leaflet to the sinotubular junction.

Sudden death has been well-reported in patients with supravalvar aortic stenosis and is believed to be precipitated by acute coronary ischemia. The risk of sudden death in patients with Williams-Beuren syndrome is estimated to be 1 in 1000 patient years, and is 25–100 times higher compared to an age-matched control population [44]. Hypertension is also common, even in the absence of renal artery stenosis [45].

Clinical Features

The diagnosis of supravalvar aortic stenosis is typically made in an asymptomatic patient who presents after ausculatation of a heart murmur. Patients with Williams-Beuren syndrome may be diagnosed due to their non-cardiac manifestations including dysphmorphic facies, intellectual disability, or hypercalcemia.

Investigations

Electrocardiogram

Electrocardiogram will typically be normal or show left ventricular hypertrophy with or without strain repolarization changes. Ischemic ST or T wave changes at rest or during exercise testing should raise the suspicion of impaired coronary arterial perfusion.

Chest Radiograph

Chest radiograph is typically normal in patients with supravalvar aortic stenosis, and is not used routinely as part of diagnostic work-up.

Echocardiogram

Transthoracic echocardiogram with Doppler is the initial imaging modality for diagnosis of supravalvar aortic stenosis. Both the standard and “high-right” parasternal long-axis imaging planes will display the discrete or “hour-glass” narrowing of the ascending aorta, typically at or near the sinotubular junction. Turbulence is identified by color Doppler, and the velocity of flow can be quantified by spectral Doppler. Similar to valvar aortic stenosis, the estimated pressure gradient across the stenosis by echocardiogram is used to grade the severity of obstruction and guide decisions regarding timing of intervention.

Echocardiogram may also demonstrate abnormalities of the aortic valve leaflets, including tethering of the leaflets at the sinotubular junction. The ascending aorta, aortic arch, and proximal descending aorta may also be diffusely hypoplastic (Fig. 91.2). Careful interrogation of the coronary arteries with 2D imaging and color Doppler can assess for ostial stenosis. Stenosis may also be evident when imaging the proximal branch pulmonary arteries. Systolic function and presence of hypertrophy of the left and right ventricles also influence decision about timing of intervention.

Magnetic Resonance Imaging and Computed Tomography

Despite the diagnostic accuracy of echocardiogram, additional non-invasive imaging is often required to assess the degree of anatomic narrowing in the ascending aorta, as well as evaluate for stenosis is other parts of the arterial tree. Both magnetic resonance imaging and computed tomography can provide excellent anatomic detail (Fig. 91.3). When coronary stenosis or insufficiency is suspected, magnetic resonance imaging may identify myocardial perfusion abnormalities or abnormal tissue characteristics to suggest previous injury.

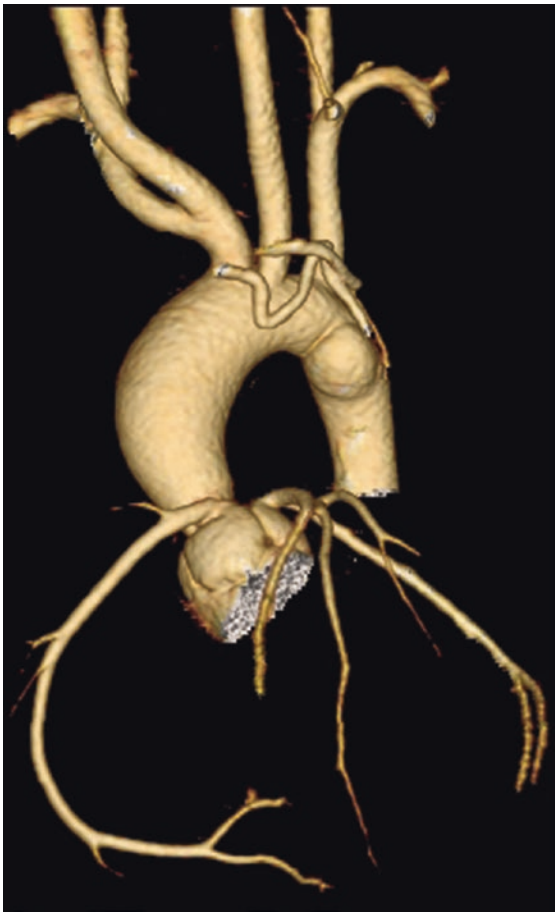

Fig. 91.3 CT angiogram of a patient with supravalvar aortic stenosis. There is severe narrowing at the sinotubular junction above the level of the coronary arteries. Note the normal sized aortic root

Cardiac Catheterization

Cardiac catheterization is typically not required for diagnosis of supravalvar aortic stenosis given the accuracy and resolution of non-invasive imaging modalities. However, direct pressure measurements may be useful when there are multiple levels of obstruction, to help inform decisions about timing of intervention in certain cases.

Management

Intervention is indicated in the setting of moderate or severe supravalvar aortic stenosis associated with symptoms of exercise intolerance, progressive aortic valve insufficiency, inducible myocardial ischemia, and/or left ventricular dysfunction. In asymptomatic patients with normal cardiac function, elective intervention may be considered when pressure gradients by echocardiogram or cardiac catheterization are significantly elevated (i.e. ≥40 mmHg), in order to decrease the risk for coronary artery atherosclerosis, damage to the aortic valve, left ventricular dysfunction, and sudden death.

Transcatheter intervention with balloon and stent placement has been described for treatment of supravalvar aortic stenosis [46]. However, due to risk for injury to the aortic valve and coronary arteries, surgical intervention is preferred.

The goal of surgical intervention is to achieve a symmetric enlargement of the aortic root and other narrowed segments of the aorta and head vessels. Concomitant stenosis of central pulmonary artery and/or coronary arteries should also be addressed during the procedure if indicated. Aortic valve repair may also be required.

Long-Term Outcomes

Severe generalized arterial forms and associated aortic valve disease are correlated with late death and the need for reoperation. The long term survival rate is between 70% and 97% and freedom from reoperation is about 65% at 20 years. Reoperations are more often due to aortic valve problems than progressive supravalvar aortic stenosis. Reoperation also appears more common in non-syndromic forms compared to patients with Williams-Beuren syndrome [45]. However, quality of life is generally good, with the majority of patients in the New York Heart Association functional class I [47].

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Atrial Septal Defects

Iman Naimi and Jason F. Deen

High Yield Facts

- Atrial septal defects (ASDs) are among the most common forms of congenital heart disease.
- Fifty percent will require surgical or transcatheter device closure.
- Thirty percent have associated cardiovascular anomalies.
- Longstanding unrepaired hemodynamically significant ASDs are associated with atrial arrhythmias, pulmonary hypertension and right heart failure.
- Transthoracic echocardiogram is most often adequate for diagnosis of the type of ASD and for associated anomalies.
- Secundum ASDs with adequate anatomic features may be closed via transcatheter device, while other types require surgical closure.
- Complications of device closure include device malposition, embolization, endocarditis, heart block and atrial or aortic erosion.
- Complications of surgical closure include postcardiotomy syndrome and endocarditis.

Introduction

Atrial septal defects (ASDs) are among the more common congenital heart defects. Shunting across the defect occurs from the left to the right atrium in the absence of right ventricular compliance abnormalities. Complications are related to the volume and duration of shunting. Approximately 50% of ASDs are treated via surgical or transcatheter means, while the remainders close spontaneously or are hemodynamically insignificant [1].

ASDs, in general, make up 7–10% of all congenital heart disorders [2]. Secundum ASDs are the most common (75%), followed by primum (15–20%) and sinus venosus ASDs (5–10%) (Fig. 92.1). Secundum ASDs are caused by deficiency of atrial septal tissue in the region of fossa ovalis [3], caused by excessive apoptosis of the cephalic portion of the septum primum with incomplete development of septum

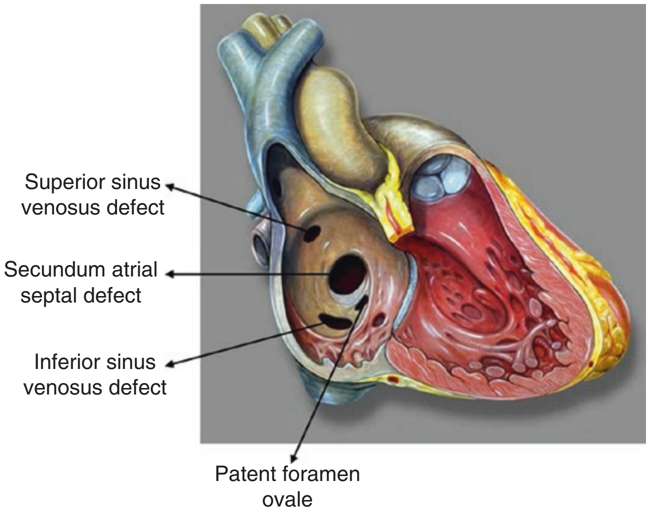
Superior sinus venosus defect
Secundum atrial septal defect
Inferior sinus venosus defect
Patent foramen ovale

Fig. 92.1 Anatomy of atrial septal defects seen from the right atrium. (Adapted from Journal of Structural Heart Disease [Buber J, Cheatham JP, Berman DP. Atrial Septal Defects: Special Considerations in Management and Closure in the Adult Patient Population. Journal of Structural Heart Disease 2016;2:46], with permission)

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secundum [4]. Primum ASDs are discussed in detail in Chap. 105. They are positioned inferiorly at the crux [3] and stem from a lack of fusion between the septum primum and the endocardial cushions [4]. Sinus venosus ASDs are located most commonly in a posterior-superior portion, straddling the inter-atrial septum at the opening of the superior vena cava; less commonly at the inferior vena cava orifice [3]. They are caused by malposition of the respective vena cava into the right atrium with deficiency in the vascular wall that separates the atrium from the right-sided pulmonary veins [4]. Thirty percent of patients with ASDs have associated cardiovascular anomalies, including partial anomalous pulmonary venous return with sinus venosus ASDs, cleft mitral valve with primum ASDs (partial atrioventricular septal defect), and valvar pulmonary stenosis with secundum ASDs.

Clinical Features

Depending on their size, secundum ASDs may spontaneously close over time, while other types generally do not [5]. Defects that are <5 mm are more likely to close spontaneously, whereas those ≥8–10 mm persist [5–7]. ASDs lead to asymptomatic right sided heart dilation [2]. However, if left unrepaired, may be associated with fatigue, dyspnea, and exercise intolerance in the adolescent or young adult. Longstanding hemodynamically significant ASDs are associated with atrial arrhythmias and, in rare cases, pulmonary hypertension and right heart failure [8]. Untreated ASD is also a risk factor for paradoxical embolisms that could lead to stroke and transient ischemic attack (TIA).

Diagnosis

Echocardiogram

Transthoracic Echocardiogram (TTE)

TTE is the primary method used in diagnosing the type and size of ASDs as well as direction and degree of shunting [4] (Fig. 92.2). It also allows diagnosis of associated lesions and assessment of the size of right-sided structures [5]. Intravenous agitated saline can be used as an adjunct contrast study to assess for presence of right to left shunt if echocardiographic images are inadequate [3, 5]. While TTE provides adequate images for most ASDs, it may be limited when used to assess sinus venosus ASDs.

Transesophageal Echocardiogram (TEE)

Given the location of atrial septum, TEE may provide better image quality compared to TTE and is used in the operating suite and cardiac catheterization laboratory to aid in ASD closure and when TTE doesn't provide adequate assessment of the defect.

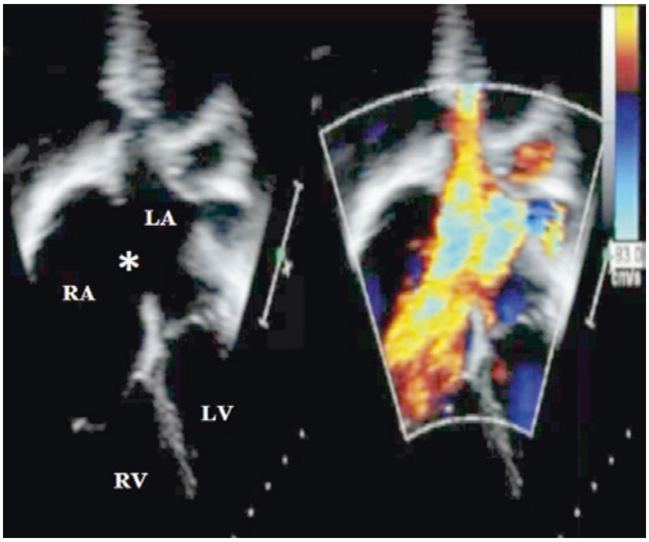

Fig. 92.2 Transthoracic echocardiogram. Apical four chamber view showing large secundum ASD (asterisk) on 2D image (left). Color compare image (right) shows left to right shunting across the defect. *RA* right atrium, *LA* left atrium, *RV* right ventricle, *LV* left ventricle. (Adapted from Journal of Structural Heart Disease [Buber J, Cheatham JP, Berman DP. Atrial Septal Defects: Special Considerations in Management and Closure in the Adult Patient Population. Journal of Structural Heart Disease 2016;2:46], with permission)

Intracardiac Echocardiogram (ICE)

Used in the cardiac catheterization laboratory to aid transcatheter device closure (Fig. 92.3), ICE provides excellent image quality but its use is limited in smaller children given the requirement for large sheaths needed to insert the ICE catheter [9].

Cross Sectional Imaging

Contrast enhanced cardiac computed tomography (CT) and magnetic resonance imaging (MRI) correlate well with TEE and are utilized to obtain high resolution images when only limited evaluation of a suspected ASD is achieved with TTE [4]. CT has higher spatial resolution and provides better assessment of the ASD morphology and its associated anomalies but its use is limited due to radiation exposure [3, 5]. MRI is an alternate method in these situations and in addition to allowing visualization of the ASD and associated defects in high resolution (Fig. 92.4), it allows for better quantification of intracardiac shunting, right ventricular (RV) volume and RV function as compared to CT [4]. Given the substantially longer time required to acquire MRI images, it is more suitable for older children and adults [4, 5, 10].

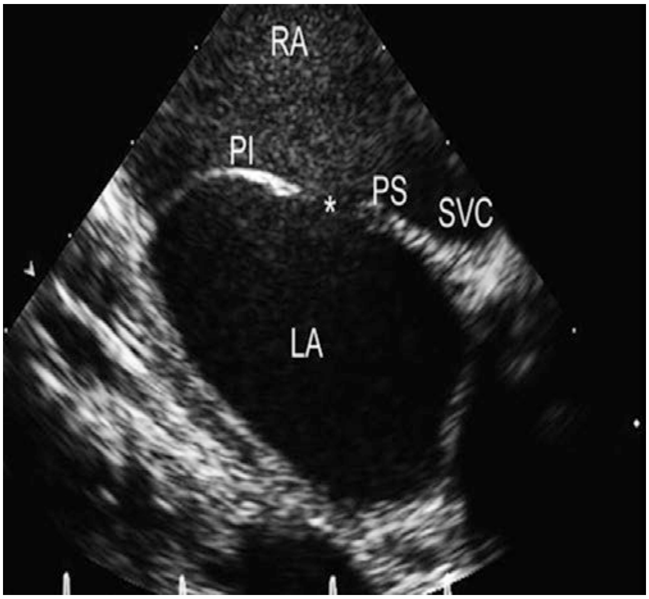

Fig. 92.3 Intracardiac Echocardiogram (ICE) showing central secundum ASD with adequate posterior-inferior rim (PI) and posterior-superior rim (PS). *RA* right atrium, *LA* left atrium, *SVC* superior vena cava. (Adapted from Journal of Structural Heart Disease [Buber J, Cheatham JP, Berman DP. Atrial Septal Defects: Special Considerations in Management and Closure in the Adult Patient Population. Journal of Structural Heart Disease 2016;2:46], with permission)

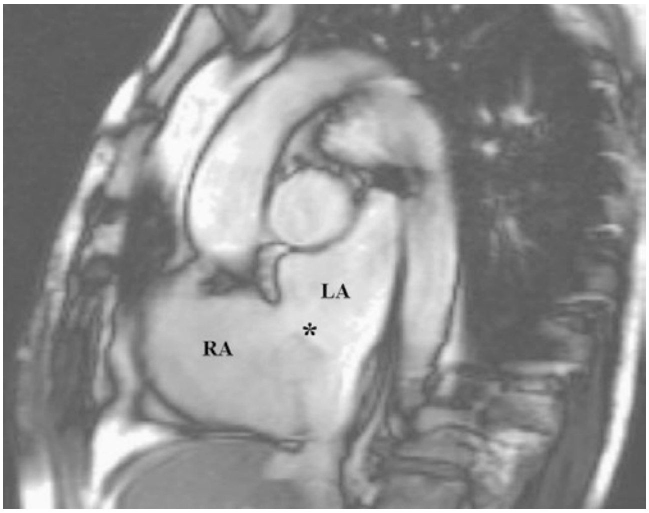

Fig. 92.4 MRI. Oblique sagittal short axis view showing large secundum ASD (asterisk). *RA* right atrium, *LA* left atrium. (Adapted from Journal of Structural Heart Disease [Buber J, Cheatham JP, Berman DP. Atrial Septal Defects: Special Considerations in Management and Closure in the Adult Patient Population. Journal of Structural Heart Disease 2016;2:46], with permission)

Cardiac Catheterization

In the modern era, cardiac catheterization is performed in the setting of transcutaneous device closure or when pulmonary hypertension is suspected [11]. It is otherwise not indicated as a diagnostic tool when non-invasive imaging has provided adequate assessment of the defect [3, 5, 10].

Indications and Timing for ASD Closure

Hemodynamically significant ASDs (as evidenced by right-sided cardiac enlargement, Fig. 92.5) should be electively closed at 4–5 years of age, even in an in asymptomatic patient to decrease the chance for development of atrial arrhythmia and to prevent symptom development in late adolescence and pulmonary arterial hypertension (PAH) in adulthood. These defects should be closed sooner in patients who develop symptoms at younger age [12].

Surgical Versus Transcatheter Management

Surgical management of ASDs became the gold standard for treatment after description of cardiopulmonary bypass technique in 1950s by Gibbon et al. Subsequently, after being first described in 1976 by Mills and King, transcatheter closure has become the treatment modality of choice in secundum ASDs [2, 13] (Figs. 92.6, 92.7, 92.8 and 92.9), while surgical closure remains the gold standard for other types of defects [14, 15].

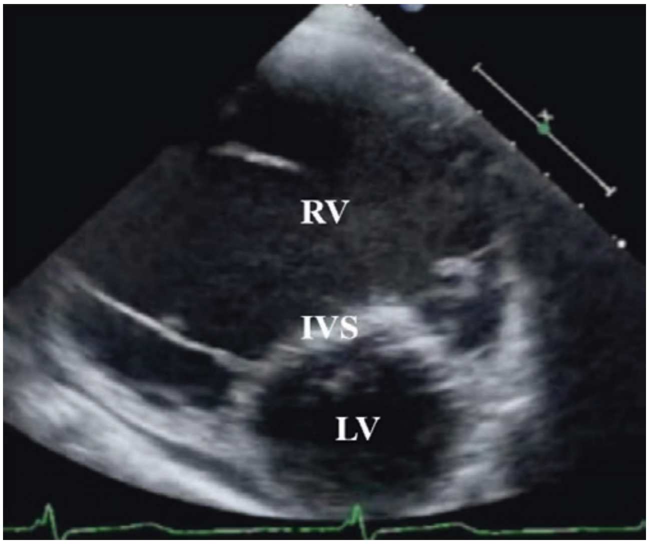

Fig. 92.5 TTE. Parasternal short axis view showing right ventricular (RV) enlargement with diastolic flattening of the interventricular septum (IVS) secondary to volume overload in patient with unrepaired ASD (not shown). *LV* left ventricle. (Adapted from Journal of Structural Heart Disease [Buber J, Cheatham JP, Berman DP. Atrial Septal Defects: Special Considerations in Management and Closure in the Adult Patient Population. Journal of Structural Heart Disease 2016;2:46], with permission)

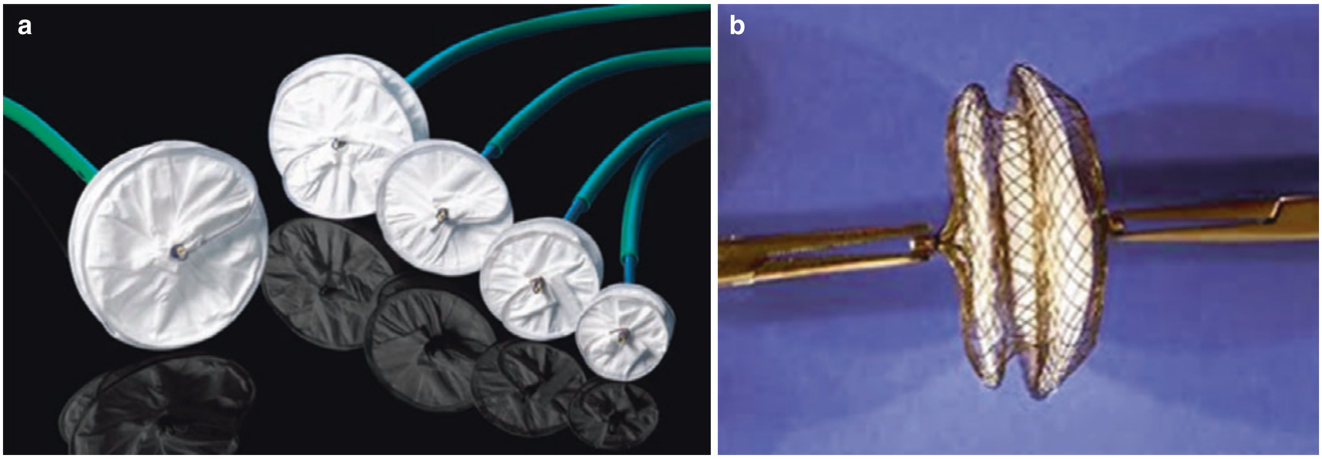

Fig. 92.6 (**a**) Gore Helix Septal Occluder and (**b**) Amplatzer ASO (Atrial Septal Occluder). (Adapted from Journal of Structural Heart Disease [Buber J, Cheatham JP, Berman DP. Atrial Septal Defects: Special Considerations in Management and Closure in the Adult Patient Population. Journal of Structural Heart Disease 2016;2:46], with permission)

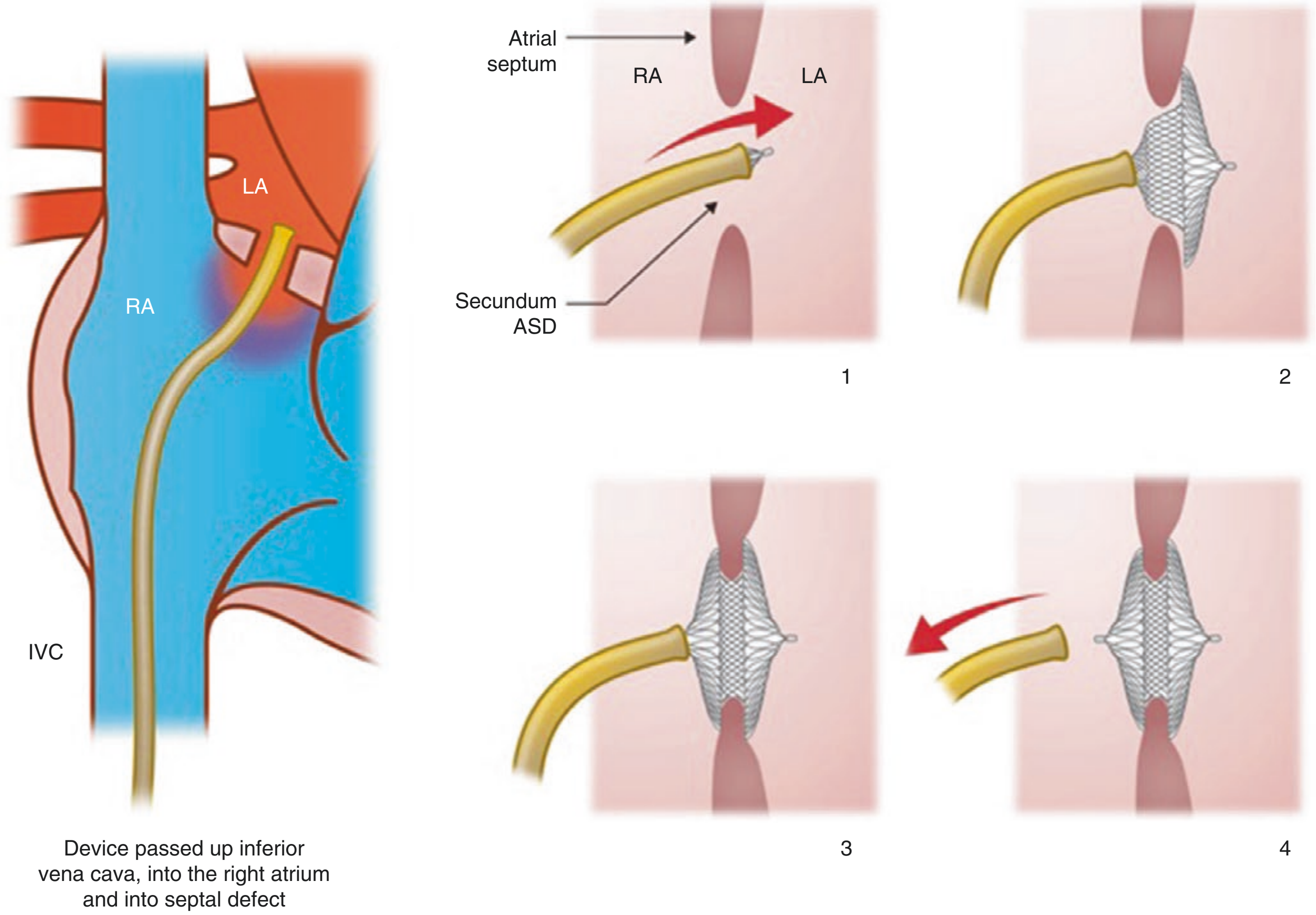
LA
RA
IVC
Device passed up inferior vena cava, into the right atrium and into septal defect
Atrial septum
RA
LA
Secundum ASD
1
2
3
4

Fig. 92.7 Transcatheter device closure of secundum ASD. (1) Device loaded catheter is passed through the atrial septum. (2) The left atrial disk is extruded and pulled back against the interatrial septum to confirm adequate device size. (3) The catheter is further pulled back to extrude the waist followed by the right atrial disk. (4) After confirming adequate placement, the device is deployed and the catheter is retracted

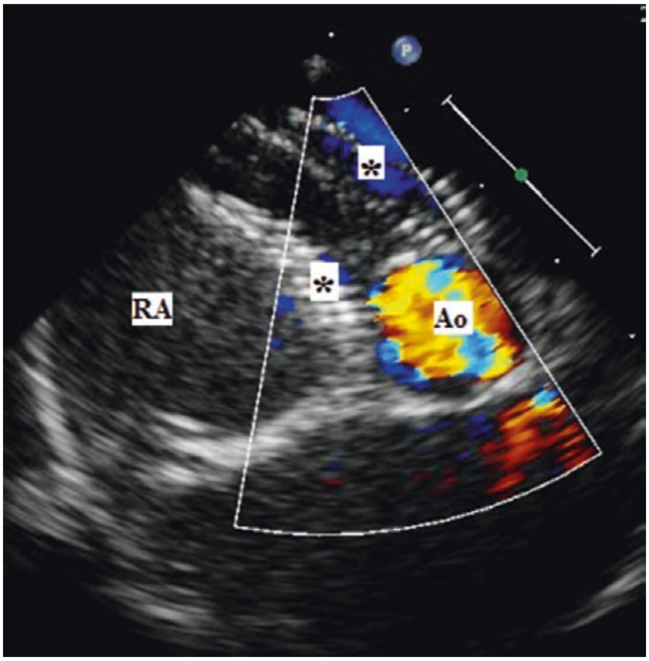

Fig. 92.8 TEE guided ASO placement showing device seated well across the defect with left and right atrial disks seated well in position (asterisk) and trivial residual shunting through the device. *RA* right atrium, *Ao* aorta. (Adapted from Journal of Structural Heart Disease [Buber J, Cheatham JP, Berman DP. Atrial Septal Defects: Special Considerations in Management and Closure in the Adult Patient Population. Journal of Structural Heart Disease 2016;2:46], with permission)

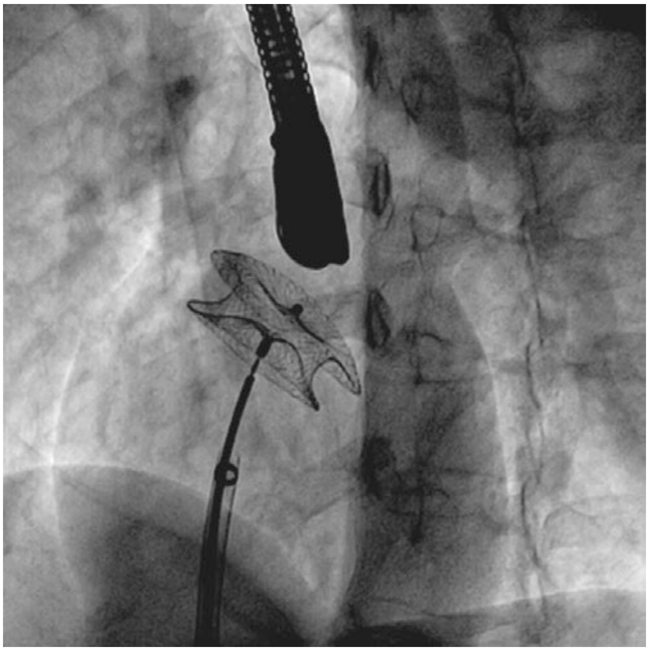

Fig. 92.9 Fluoroscopic view of ASO in left anterior oblique (LAO) angulation confirming device position across the ASD prior to release from loading cable. (Adapted from Journal of Structural Heart Disease [Jain S, Dalvi B. Atrial Septal Defect: Step-by-Step Catheter Closure. Journal of Structural Heart Disease 2016;Volume 2(1):15–32. https://doi.org/10.12945/j.jshd.2016.007.1], with permission)

Surgical and Interventional Therapy Recommendations

The recommendations for surgical and transcatheter closure of ASDs are outlined by the American Heart Association (AHA) [2, 3].

Class	Recommendation	Level of evidence
I	Closure of an ASD either percutaneously or surgically is indicated for RA and RV enlargement with or without symptoms.	B
I	Transcatheter device closure is indicated in patients with sASD who have a hemodynamically significant[a] defect with suitable anatomic features[b].	B
I	Sinus venosus, coronary sinus, or primum ASD should be repaired surgically rather than by percutaneous closure.	B
I	Surgeons with training and expertise in CHD should perform operations for various ASD closure.	C
IIa	Surgical closure of sASD is reasonable when concomitant surgical repair/replacement of a tricuspid valve is considered or when the anatomy of the defect precludes the use of a percutaneous device.	C
IIa	Closure of an ASD, either percutaneously or surgically, is reasonable in the presence of documented orthodeoxia-platypnea.	B
IIa	Closure of an ASD, either percutaneously or surgically, is reasonable in the presence of paradoxical embolism.	C
IIb	Closure of an ASD, either percutaneously or surgically, may be considered in the presence of net left-to-right shunting, pulmonary artery pressure less than two thirds systemic levels, PVR less than two thirds systemic vascular resistance, or when responsive to either pulmonary vasodilator therapy or test occlusion of the defect (patients should be treated in conjunction with providers who have expertise in the management of pulmonary hypertensive syndromes).	C
IIb	Concomitant Maze procedure may be considered for intermittent or chronic atrial tachyarrhythmias in adults with ASDs.	C
IIb	Transcatheter closure may be considered in patients with a small sASD who are believed to be at risk of thromboembolic events (e.g., patients with a transvenous pacing system or chronically indwelling intravenous catheters, patients with hypercoagulable states).	C
III	Patients with severe irreversible PAH and no evidence of a left-to-right shunt should not undergo ASD closure.	B
III	Transcatheter sASD closure is not indicated in patients with a small sASD of no hemodynamic significance and with no other risk factors.	B
III	Transcatheter ASD closure should not be performed with currently available devices in patients with ASDs other than secundum type (i.e.: septum primum, sinus venosus defects, and unroofed coronary sinus defects) and in patients with sASD and advanced pulmonary vascular obstructive disease.	C

[a] Right-sided heart volume overload, right-sided heart failure, and/or elevation of right-sided heart pressures

[b] Surrounded by adequate septal rims to ensure device stability and to allow the device to sit well in place without interference from vital cardiac structures such as pulmonary veins and atrioventricular valves

Surgical Techniques and Results

Surgical ASD closure was first performed by Murray in 1948 using an external suture technique without direct visualization of the defect. Subsequently, in 1953, Gibbon performed the first closure using open technique that allowed for direct visualization of the defect. Currently, small to moderate size ASDs are repaired by direct suture closure and larger defects usually require patch closure (autologous pericardial or synthetic) [16].

Traditional Surgical Closure

ASD closure historically has been achieved through median sternotomy (Fig. 92.10) and partial lower sternotomy in children younger than 3 years of age [17, 18]. Although these procedures are safe (mortality less than 1%), the morbidity associated with sternotomy/thoracotomy and bypass is unavoidable, and are associated with higher costs and longer hospital length of stay compared to transcatheter closure.

Minimally Invasive Cardiac Surgery

More recently, minimally invasive cardiac surgery (MICS) has been utilized in ASD closure by creating small skin incision in the right chest wall (right mini-thoracotomy) from where endoscopic surgery is performed [19, 20]. Since this technique does not require full sternotomy, it is cosmetically appealing and allows for faster recovery and subsequently decreases costs [21, 22]. In a study comparing transcatheter device closure and ASD closure by MICS, both techniques had high success rate without reported mortality. However, given increased chance of both minor (11.2% vs. 20.9%, respectively) and major (1.5% vs. 3.6%, respectively) complications in the MICS group, percutaneous technique in patients with suitable anatomy is recommended. Totally robotic MICS has been performed successfully and has the potential to become the therapeutic choice in the future for ASD closure in patient who are not transcatheter device closure candidates [23–25].

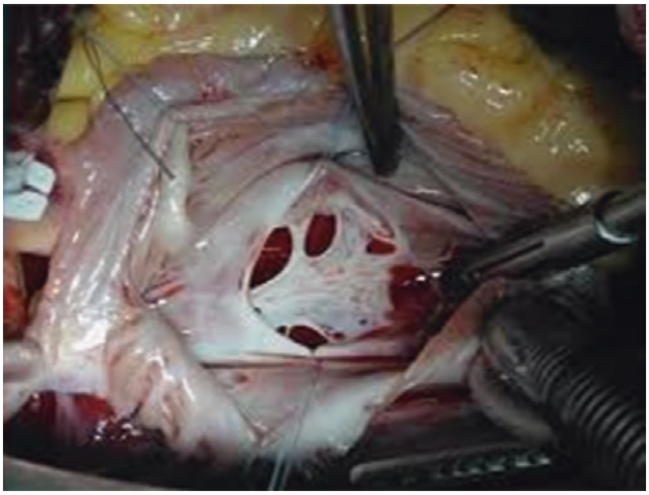

Fig. 92.10 Median sternotomy showing fenestrated atrial septum through right atrial incision. (Adapted from Journal of Structural Heart Disease [Management and Closure in the Adult Patient Population. Journal of Structural Heart Disease 2016;2:46], with permission)

Right Axillary Incision Approach

Right axillary incision is an alternate approach suggested for patients with suitable anatomy that can be used in smaller infants as it utilizes central instead of peripheral cannulation for cardiopulmonary bypass [26]. It has been shown to be safe and effective with no reported intraoperative deaths or requirement to convert to sternotomy. In-hospital complications include mortality (0.3%), re-operation for bleeding (1%), pneumothorax or pleural effusion (2%) and requirement for permanent pacemaker placement (1%).

Secundum ASD

Surgical closure of secundum ASD carries negligible operative morbidity and mortality (<1%) if PVR is normal. Long-term outcomes are determined by patient's age and pulmonary artery pressures at the time of surgery. Older age and high pulmonary artery pressures are independent risk factors for poor-outcome [27]. Long-term survival in patients who are younger than 24 years at the time of surgery is similar to controls. However, survival is decreased significantly in patients who undergo repair between 25 and 41 years as compared to controls (84% vs. 91%). This is further decreased if repair is performed after age 41 (40% vs. 59%). A potential complication in surgical repair of these defects includes inadvertent attachment of the Eustachian valve to the atrial septum leading to right to left shunting requiring re-operation.

Primum ASD

Discussed in Chap. 105.

Sinus Venosus ASD

Sinus venous ASDs can simply be repaired using autologous pericardial patch if they are not associated with anomalous pulmonary veins. However with partial anomalous pulmonary veins, venous return has to be re-directed to the left atrium in addition to ASD closure. These patients are at risk for long-term complications including superior vena cava stenosis, pulmonary vein orifice obstruction, sinus node dysfunction and atrial arrhythmias. Redirection of the anomalous pulmonary vein to the left atrium may be achieved via an intranasal [28] or transcaval technique [29–31].

Warden Procedure

The Warden procedure is performed when the right pulmonary vein inserts more than 2 cm above the superior cavo-atrial junction [32]. This is carried out by transecting the superior vena cava above the entrance of anomalous pulmonary vein and connecting it directly to the right atrial appendage. The proximal superior vena cava containing the anomalous vein is then baffled to the left atrium using a patch.

Postoperative Complications

The most common postoperative complication of surgical ASD closure is postcardiotomy syndrome which is an immune response to pericardial trauma presenting with pericardial effusion with symptomatology including fever, nausea, vomiting, as well as chest and abdominal pain. This phenomenon is typically treated with nonsteroidal anti-inflammatory agents or colchicine, but corticosteroids are used in refractory cases [33, 34]. An echocardiogram should be performed to assess for pericardial effusion and to rule out tamponade. Although the incidence of atrial arrhythmia is negligible in patients who undergo repair before 40 years of age (<1%), it increases significantly when repair is performed at an older age (15% and 61% in 40–60 and >60 years, respectively); furthermore these patients are more likely to have elevated pulmonary artery pressures [35, 36]. Bacterial endocarditis is rare in patients who undergo isolated ASD closure and more likely to occur if the defect is associated with valvar disease.

Outcomes of Transcatheter Closure and Comparison with Surgical Closure

In a study comparing device closure using the Amplatzer Septal Occluder to surgical repair, it was found that there was no statistically significant difference in overall mortality or need for re-operation between the two groups. However, mortality and need for surgery per adverse event were higher in the device group (1.2% vs. 7.6%, and 3.6% vs. 68.2% respectively) [37]. Furthermore, the mortality for surgical management of a device adverse event (2.6%) was 20-times higher than for primary elective surgical closure (0.13%, $P < 0.001$). Nevertheless, transcatheter closure has been found to be effective and durable over long-term with initial success rate and long-term objective efficacy of 100%. Furthermore, 95% of patients experienced subjective symptomatic relief at 1 year follow-up from device placement. ASD device closure carries a lower rate of post-procedure complications and shorter hospital length of stay compared to surgical repair. Given the reliability, ease of operation, short anesthesia time and hospital length of stay, and low complication rates, ASD device closure is the procedure of choice in secundum ASD treatment [38–41].

Catheter Closure of ASD Compared to Minimally Invasive Cardiac Surgery

In a study comparing outcomes of ASD closure by MICS versus catheter based techniques, both procedures were highly successful (MICS 100%, transcatheter 98%). There were no deaths in either group although there were more major and minor complications in the MICS group (3.6% versus 1.5%; $P = 0.16$ and 20.9% vs. 11.2%; $P = 0.02$, respectively). Although both of these techniques are highly successful without reported mortality, in patients with suitable anatomy, device closure is usually considered the first therapeutic option.

Early Complications of ASD Devices

Early complications associated with ASD devices are rare. These include device malposition and migration (Fig. 92.11), cardiac perforation leading to tamponade and death, and atrioventricular block Complications from cardiac catheterization itself including air embolism, infection, and hematomas have also been reported.

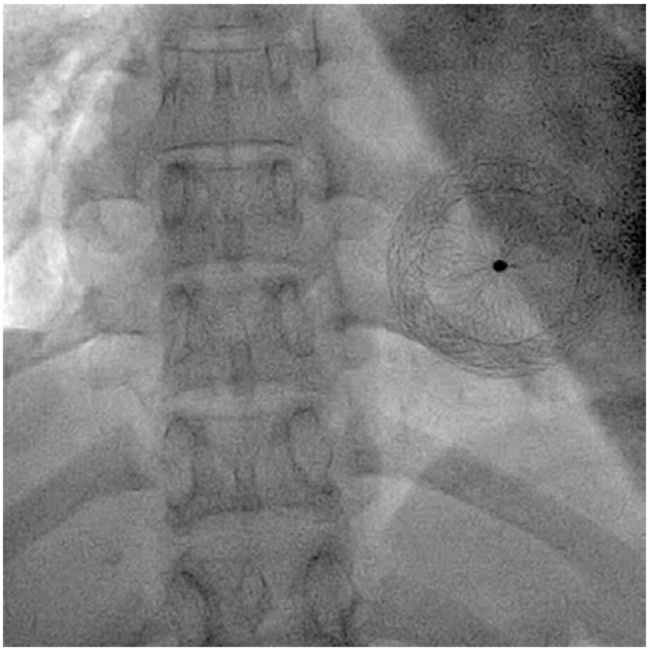

Fig. 92.11 Fluoroscopic straight frontal view of embolized ASO device in the right ventricle. (Adapted from Journal of Structural Heart Disease [Jain S, Dalvi B. Atrial Septal Defect: Step-by-Step Catheter Closure. Journal of Structural Heart Disease 2016;Volume 2(1):15–32. https://doi.org/10.12945/j.jshd.2016.007.1], with permission)

Late Complications of ASD Devices

The most common mechanism of late complication is atrial and aortic erosion adjacent to the device, though this risk is attenuated in the modern era with standardized intraprocedural sizing techniques [37, 42, 43]. Devices are expected to endothelialize within 6 months after deployment, therefore, antibiotic prophylaxis is recommended for that time period. There have been rare case reports of endocarditis late after device closure due to incomplete endothelialization. Most of these cases have been associated with other cardiac abnormalities [44, 45].

Conclusion

Atrial septal defects are the third most common type of CHD. Included in this group of malformations are several types of atrial communications that allow shunting of blood between the systemic and the pulmonary circulations. Most children with isolated atrial septal defects are free of symptoms, but the rates of exercise intolerance, atrial tachyarrhythmias, RV dysfunction, and PAH increase with advancing age and life expectancy is reduced in adults with untreated defects. The risk of development of pulmonary vascular disease, a potentially lethal complication, is higher in female patients and in older adults with untreated defects. Surgical closure is safe and effective and when done before age 25 years is associated with normal life expectancy. Transcatheter closure offers a less invasive alternative for patients with a secundum defect who fulfil anatomical and size criteria.

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93

Isolated Ventricular Septal Defect

Sian Chivers and Attilio A. Lotto

High Yield Facts

- Isolated ventricular septal defect (VSD) accounts for 37% of all congenital heart disease in children.
- VSDs have an incidence of 3–3.5 per 1000 live births.
- As many as 90% VSDs may eventually close spontaneously.
- VSDs have no gender predilection.
- Perimembranous VSD is, by far the most common type, accounting for 80% of all defects.
- The size of VSD is described in comparison to the diameter of the aortic annulus. They are considered small if they measure less or equal to 25% of the aortic annulus diameter, medium if they measure more than 25% but less than 75%, and large if they are greater than 75% of the aortic annulus diameter.
- Approximately 85–90% of small isolated VSDs close spontaneously during the first year of life.
- Without pulmonary arterial hypertension (PAH), the operative mortality rate is approximately 1%.
- Percutaneous device closure is reserved for those in whom surgery is very risky due to severe PAH, multiple comorbidities, and those with residual or recurrent VSD after surgical closure.

Introduction

Isolated ventricular septal defect (VSD) implies congenital heart disease where there is a defect in the interventricular septum with no associated morphological abnormalities. The differing anatomical variants result in diverse haemodynamic consequences and require different surgical approaches. The first successful surgical closure was performed in 1955 by Lillehei et al. [1] since which time it has become one of the most common operations performed by congenital cardiac surgeons, with intervention on more complex defects, in smaller patients and with newer surgical techniques being developed.

Complete surgical repair of the defect by patch closure is the most common approach, but in specific cases there remains a role for pulmonary artery banding (PAB), for example in multiple muscular VSDs. The use of PAB has however decreased significantly in the last few decades. Trans-catheter and hybrid device closure is becoming more common with encouraging results reported in the literature [2, 3].

This chapter will focus on the classification and pathophysiology of isolated VSD, with detailed information on the operative approach and further discussion on newer interventions to repair isolated VSD.

Epidemiology

Isolated VSD is the commonest congenital heart defect with an incidence of 3–3.5 per 1000 live births [4] and accounts for 15–20% of all congenital heart disease. Published studies suggest that the incidence of isolated VSD has increased over time representing either a true increase or increased sensitivity of detection with newer imaging techniques.

The majority of VSDs are not linked to an underlying genetic abnormality; however there is an increased incidence of isolated VSD in patients with Down's syndrome, other trisomies such as trisomy 18, trisomy 13 and in the 22q11 microdeletion syndrome.

Survival after surgical intervention is excellent across the developed world. Data from the National Institute for Cardiovascular Outcome Research (NICOR) show that during the period 2014–2017, there were 1005 patients operated

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in the United Kingdom (UK) for isolated VSD closure with only one death, for 99.9% 30-day survival rate [5].

Morphology

The left and right ventricles have distinct morphological features.

The Right Ventricle (RV)

1. The tricuspid valve (TV) has three major leaflets—septal, anterosuperior and inferior.
2. The TV is separated from the pulmonary valve (PV) by a muscular ridge known as the supraventricular crest.
3. The apical trabecular component has coarse trabeculations, the most prominent of which is the septomarginal trabeculation.
4. The prominent moderator band extends from the anterior papillary muscle of the TV to the parietal wall of the RV.

The Left Ventricle (LV)

1. The mitral valve (MV) has two leaflets, an anterior and a larger posterior (or mural) leaflet with one zone of apposition.
2. The anterior leaflet of the MV is in fibrous continuity with parts of the left and non-coronary leaflets of the aortic valve (AV).
3. The septal surface of the interventricular septum is smooth.
4. The mitral valve has no chordal attachments to the interventricular septum.
5. The apical trabecular component has characteristic fine trabeculations.

Both ventricles consist of three distinct components:

- Inlet component which runs from the inlet of the atrioventricular valve to the attachments of the tensor apparatus of the valve.
- Outlet component which is the smooth walled area below the outflows of the great arteries.
- Apical trabecular component which extends from the attachments of the tensor apparatus of the atrioventricular valve to the apex of the heart with more coarse trabeculations found in the RV as compared to the LV.

The interventricular septum is a complex structure which runs superiorly from the interatrial groove by the intersection formed by the coronary sinus to the crux of the heart, with its anteroposterior boundary identified by the interventricular grooves where the left anterior descending artery runs anteriorly and the posterior descending artery runs posteriorly.

It is mainly a muscular structure, with a small membranous portion which is closely related to the septal leaflet of the TV and the AV commissure between the right and non-coronary sinus.

So anatomically a VSD can be described if it lays in the inlet, outlet or apical component of the ventricle, and if it is surrounded by muscle (muscular VSD) or if it is adjacent to the membranous septum (perimembranous VSD).

When considering the anatomy of an isolated VSD, there are numerous classifications for nomenclature including those most widely known and published by Anderson, Soto and Van Praagh [6–9].

In this chapter we will group ventricular septal defects as:

1. **Perimembranous**
2. **Muscular**
3. **Juxta-arterial**
4. **Other**

Perimembranous Ventricular Septal Defects

These are the most common type of ventricular septal defect and are mainly due to a deficiency of the membranous septum. Their diagnostic feature is the fibrous continuity between the right and non-coronary leaflets of the aortic valve and septal leaflet of the tricuspid valve. As these defects lay in such close proximity to the TV and AV, associated abnormalities of such valves are common including tethering of the septal and antero-superior leaflets of the TV or AV leaflet prolapse through the defect.

They may extend in any direction towards the inlet, apical trabecular or outlet portions of the right ventricle.

Inlet defects are positioned beneath the septal leaflet of the tricuspid valve. These defects are most commonly associated with straddling of the septal leaflet of the tricuspid valve.

Centrally opening defects open into the RV adjacent to the area of the central fibrous body and are orientated towards the cardiac apex.

Outlet defects extend into the muscular septum towards the outlet of the right ventricle and are associated with some degree of aortic override.

Muscular Ventricular Septal Defects

These defects account for 5–20% of VSDs. They may be single but are frequently multiple and are found in any portion of the muscular septum. Very small defects may go undiagnosed as they have little physiological impact. If small, they may close spontaneously. Muscular defects may also occur in addition to other forms of ventricular septal defect including perimembranous defects or juxta-arterial defects. When they are numerous they may be referred to as a “Swiss cheese” type of muscular VSDs.

Juxta-Arterial Defects

A juxta-arterial, or doubly committed subarterial defect, refers to one where there is fibrous continuity between the aortic and pulmonary valves. There is deficiency of the outlet septum and the septal component of the subpulmonary infundibulum. These defects may extend into the perimembranous or muscular septum. These defects are uncommon and represent 5–7% of surgically operated VSDs in Western populations but up to 30% within the Asian population.

Cases in which there is extension into the perimembranous region are of particular surgical importance as the conduction tissue is not protected by the presence of the trabecular septomarginalis as a landmark.

A common associated feature of juxta-arterial defects is the presence of AV right coronary cusp prolapse into the subarterial VSD. Prolapsing of the cusp may partially or completely close the defect, but this might lead to aortic insufficiency due to leaflet prolapse in diastole.

Other

A Gerbode’s defect is a rare defect within the membranous septum that leads to a true LV to right atrial connection. The defect is located high within the ventricular septum with an associated lesion of the septal leaflet of the TV. The Gerbode’s defect encompasses <1% of congenital cardiac defects [10, 11].

Pathophysiology

The pathophysiological effects of an isolated VSD are determined by the size of the defect and the pulmonary vascular resistance (PVR). Typically, an isolated VSD will exhibit left to right shunting across the defect resulting in increased blood flow to the pulmonary circulation. The size of the shunt is determined by the size of the defect and the PVR. With time, left to right shunt will lead to a number of deleterious effects on the heart and lungs, if significant. Some defects do not have a significant shunt and are known as isolated restrictive VSDs. Typically these defects do not require intervention unless they are very close to the aortic valve and might be complicated by aortic valve cusp prolapse.

- Increased left ventricular volume load
  The left to right shunt and increased pulmonary blood flow leads to increased pulmonary venous return and therefore volume load on the left heart structures. This can result in increased LV dimensions and LV end diastolic pressure (LVEDP). Ongoing increase in LVEDP has also an effect on left atrial and pulmonary venous pressure affecting the pulmonary vascular bed with interstitial fluid leak possibly leading to pulmonary oedema.
- Increased pulmonary vascular resistance
  After birth the PVR is high, but gradually decreases over the following 2–3 months. In infants with significant left to right shunt the process is prolonged. Eventually the fall in PVR will increase the left to right shunt, leading to symptoms secondary to augmented pulmonary blood flow. Over time (months or years), if intervention to reduce the left to right shunt (i.e. close the VSD) is not undertaken, the increased pulmonary blood flow will lead to changes within the pulmonary arterioles. Hypertrophy of muscle cells within the vascular wall and intimal proliferation will increase PVR, hence decreasing the left to right shunting with some improvement in symptoms. At this stage, PVR could still be reversible, and closing the VSD could still results in dropping the PVR. Nonetheless, if left untreated, PVR will equalise systemic vascular resistance (SVR) and eventually will exceed SVR resulting in a right to left shunting across the VSD with consequent cyanosis (Eisenmenger’s syndrome).

Clinical Features

The clinical presentation of the patient with a VSD will depend on the pathophysiological effects of the defect.

Small VSD

Children are usually asymptomatic. The diagnosis may be made clinically by the finding of a typical murmur (either pan-systolic or in selected cases early systolic). Others are diagnosed after an echocardiogram for an incidental murmur or during screening for example in patients with some genetic syndromes for example trisomy 21 and 22q11 microdeletion.

Large Symptomatic VSD

The effects of a significant VSD are not usually obvious in the first few days of life but present as the PVR falls when a murmur may be heard. These infants usually present with symptoms secondary to increased pulmonary blood flow for example breathlessness, poor feeding and signs of congestive cardiac failure. Clinical examination findings may include a pan-systolic murmur, increased work of breathing with costal recession and fine crepitations on the lung fields. Hepatomegaly is not uncommon and weight gain since birth may be poor. Untreated patients with a large VSD and increased PVR will present with cyanosis as the left to right shunt reverse.

Investigations

12-Lead Electrocardiography

In small VSDs, the ECG is usually normal. In infants with more haemodynamic significant VSD the ECG will show an inappropriate sinus tachycardia for age. The QRS axis may be normal but left axis deviation is seen in inlet VSDs. More commonly right axis deviation is found when pulmonary artery pressure is high. Features of biventricular hypertrophy with equiphasic QRS complexes across the precordial leads are common in large defects. An upright T wave beyond the first week of life in lead V1 is a feature of right ventricular hypertrophy. Occasionally left atrial hypertrophy is seen (Fig. 93.1).

Chest X-Ray

The chest X-ray may be normal in the first few days of life. As the left to right shunt increases, cardiomegaly is obvious and will be associated with increased pulmonary vascular markings and, in some cases, evidence of enlargement of both the main and branch pulmonary arteries. Dilatation of the left atrium increases the angle between the right and left pulmonary arteries. Lung fields are often hyperinflated and the diaphragm flattened (Fig. 93.2).

Echocardiography

A full echocardiographic assessment should be performed using the sequential segmental approach at diagnosis and as indicated by the clinician at follow up. The standard views to delineate the defect include the subcostal views, apical four and five chamber views, parasternal long and short axis and the high parasternal and suprasternal notch views.

Rate	167
PR	107
QRSD	69
QT	246
QTC	411
--AXIS--	
P	81
QRS	108
T	78

12 Lead; Standard Placement

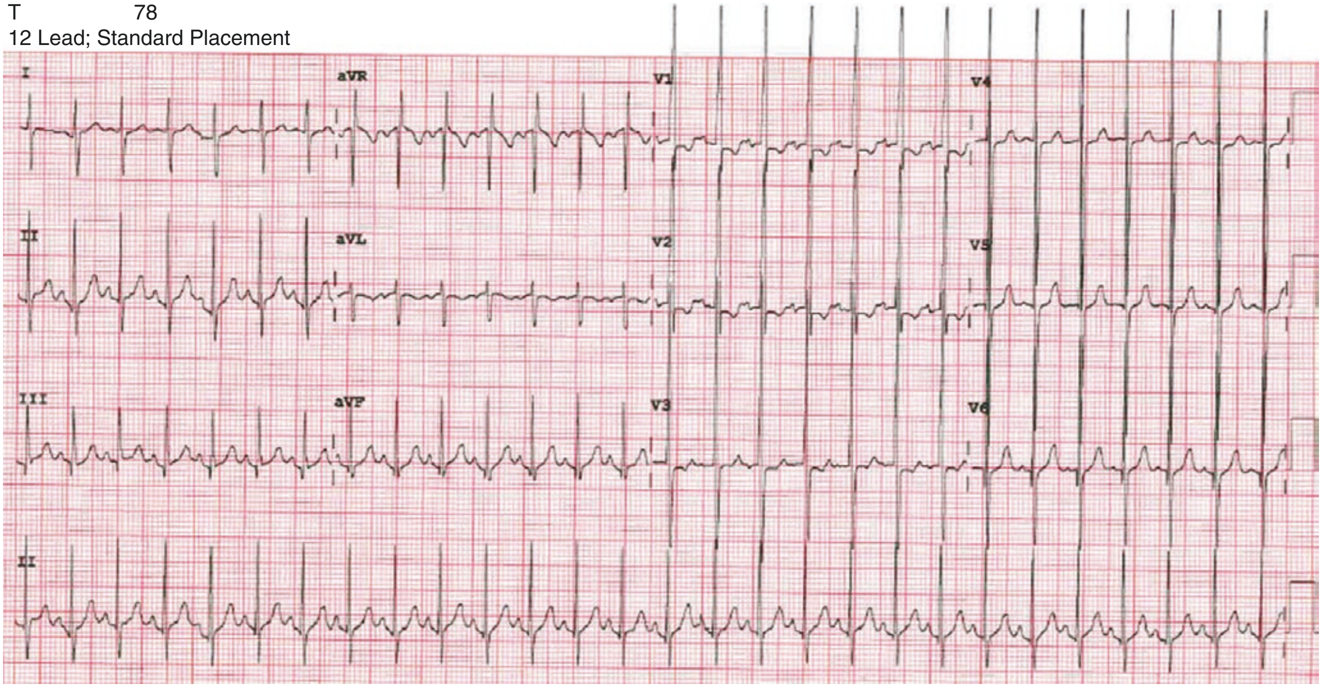


Fig. 93.1 12-Lead ECG demonstrating sinus tachycardia with biventricular hypertrophy

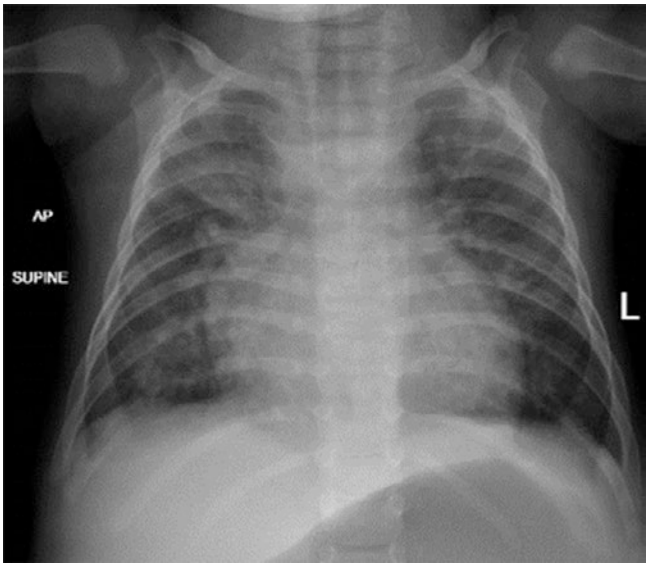


Fig. 93.2 Chest X-ray demonstrating cardiomegaly and bilateral pulmonary plethora

In some institutions three-dimensional echocardiography will be used. This approach is particularly useful in patients where there is concern surrounding location of the defect or abnormalities of the atrioventricular valves, for example straddling of the valve leaflets.

Echocardiography will delineate the location, size and number of defects and is particularly important to direct the surgical approach for closure of the defect. Colour flow and spectral Doppler can be used to assess the flow direction and indirectly assess pressures. Haemodynamic significance of the defect can be ascertained by measurement of the left ventricle and main pulmonary artery dimensions. The tricuspid and aortic valves should be thoroughly interrogated to assess for any regurgitation, prolapse or valve straddling. Ventricular size and function can be measured by two dimensional M-mode and Simpson's biplane method (Figs. 93.3, 93.4, 93.5, 93.6 and 93.7).

Transoesophageal echocardiography is used in most cases intraoperatively. Assessment of the adequacy of closure of the defect can be examined alongside ventricular function and any evidence of valvar regurgitation. Colour flow and spectral Doppler may be used as in transthoracic echocardiography.

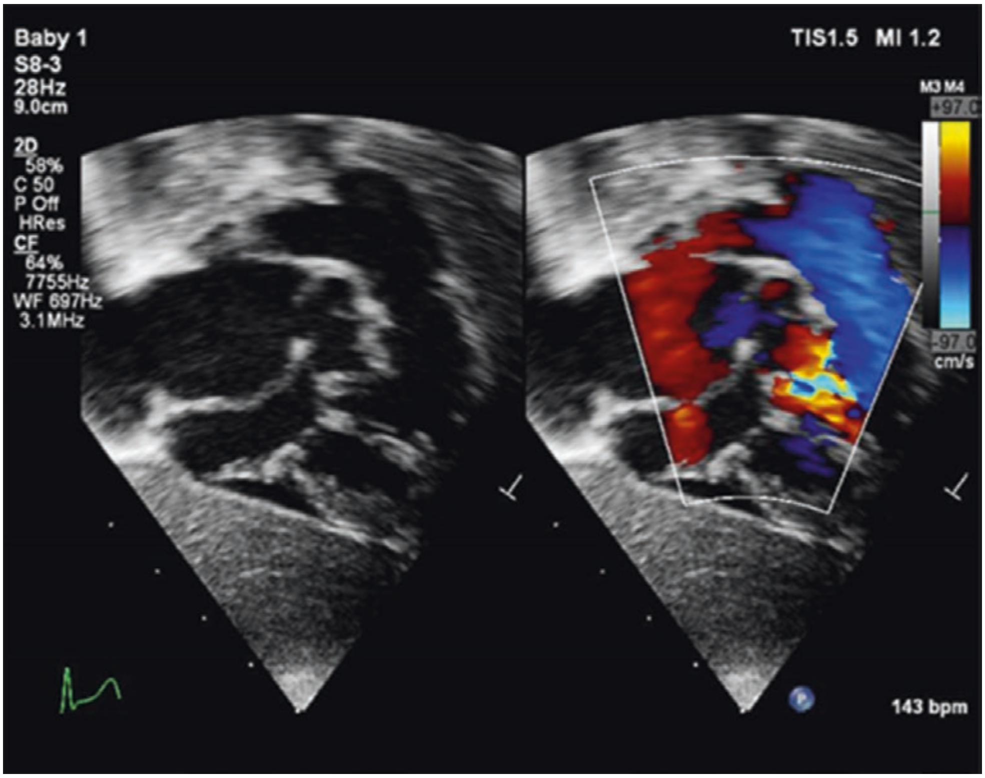


Fig. 93.3 Right subcostal oblique view demonstrating perimembranous ventricular septal defect on 2D and colour flow imaging. The size of the defect is clearly demonstrated and in addition enlargement of the main pulmonary artery

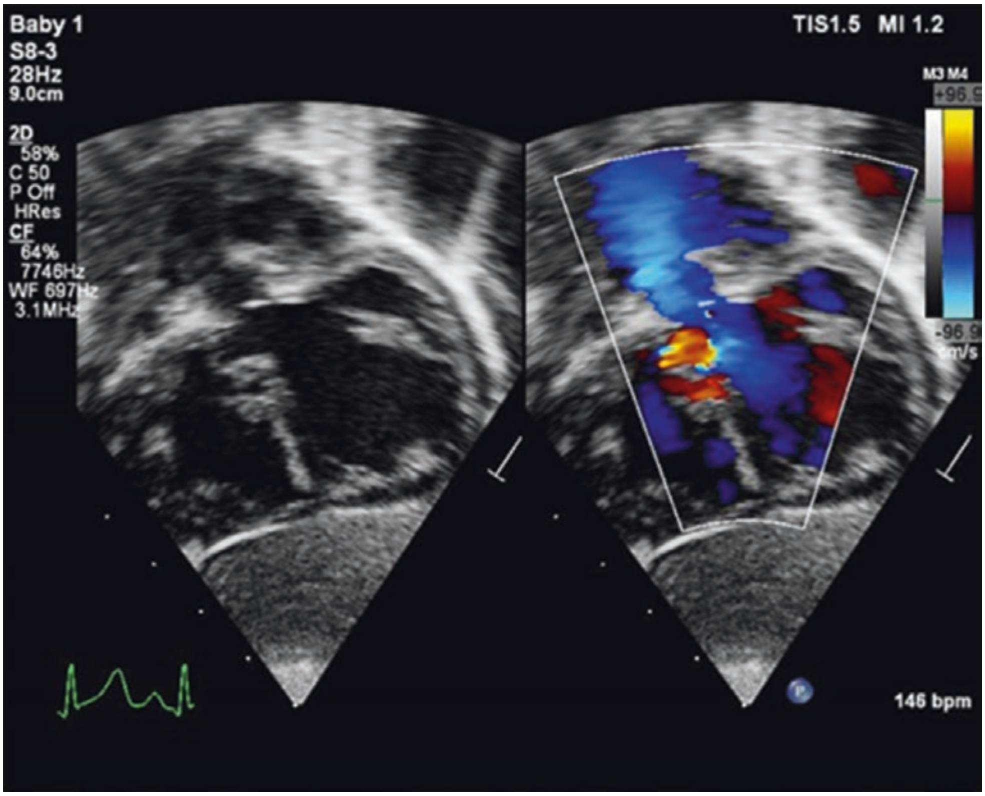

Baby 1
S8-3
28Hz
9.0cm
2D
58%
C 50
P Off
HRes
CF
64%
7746Hz
WF 697Hz
3.1MHz
TIS1.5 MI 1.2
M3 M4
+96.9
-96.9
cm/s
146 bpm

Fig. 93.4 Subcostal long axis view demonstrating perimembranous ventricular septal defect on 2D and colour flow imaging. Note the proximity of the tricuspid valve tissue, no evidence of valve straddling seen and laminal flow through the aortic valve with no evidence of aortic valve regurgitation

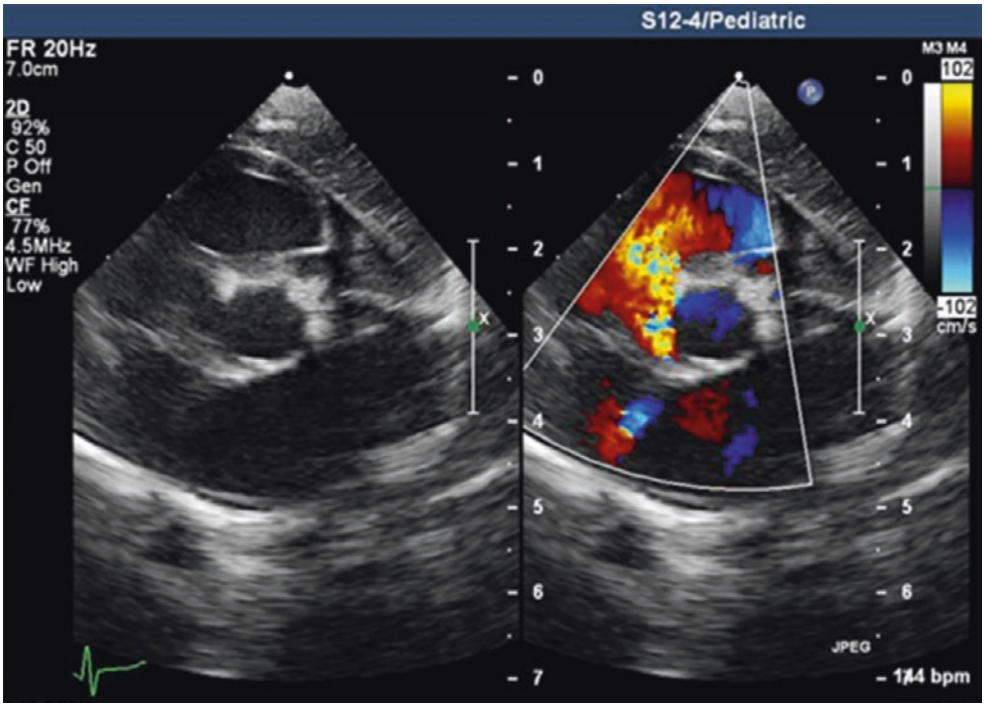
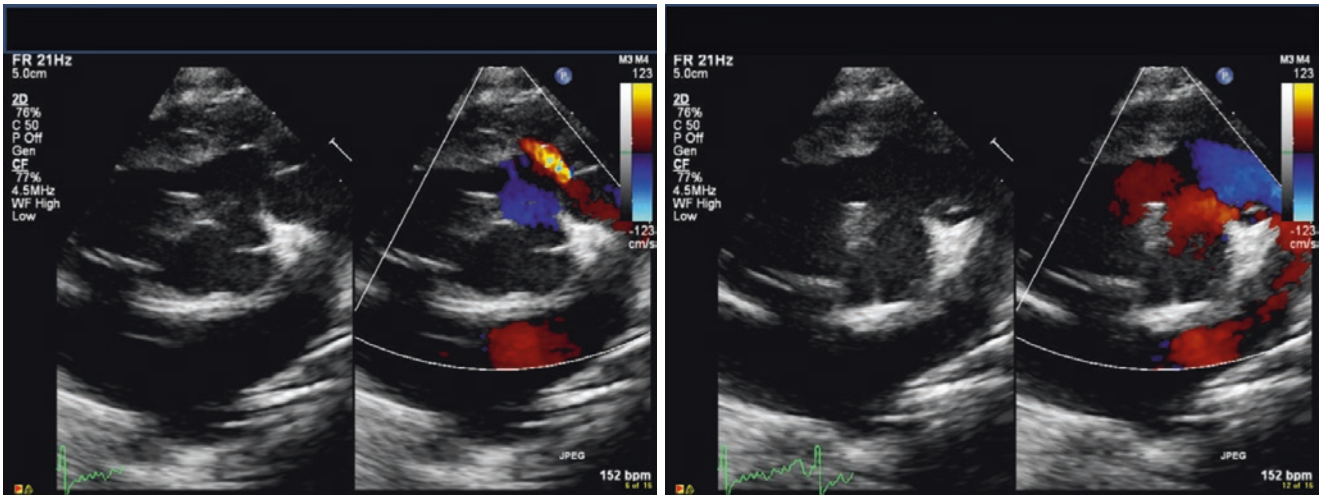

S12-4/Pediatric
FR 20Hz
7.0cm
2D
92%
C 50
P Off
Gen
CF
77%
4.5MHz
WF High
Low
M3 M4
102
-102
cm/s
0
1
2
3
4
5
6
7
JPEG
144 bpm

Fig. 93.5 Parasternal short axis image demonstrating perimembranous ventricular septal defect on 2D and colour flow imaging. This image clearly shows that there is fibrous continuity between the tricuspid and aortic valves showing that the defect is located in the perimembranous septum


FR 21Hz
5.0cm
2D
76%
C 50
P Off
Gen
CF
77%
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WF High
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123
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JPEG
152 bpm
FR 21Hz
5.0cm
2D
76%
C 50
P Off
Gen
CF
77%
4.5MHz
WF High
Low
123
-123
cm/s
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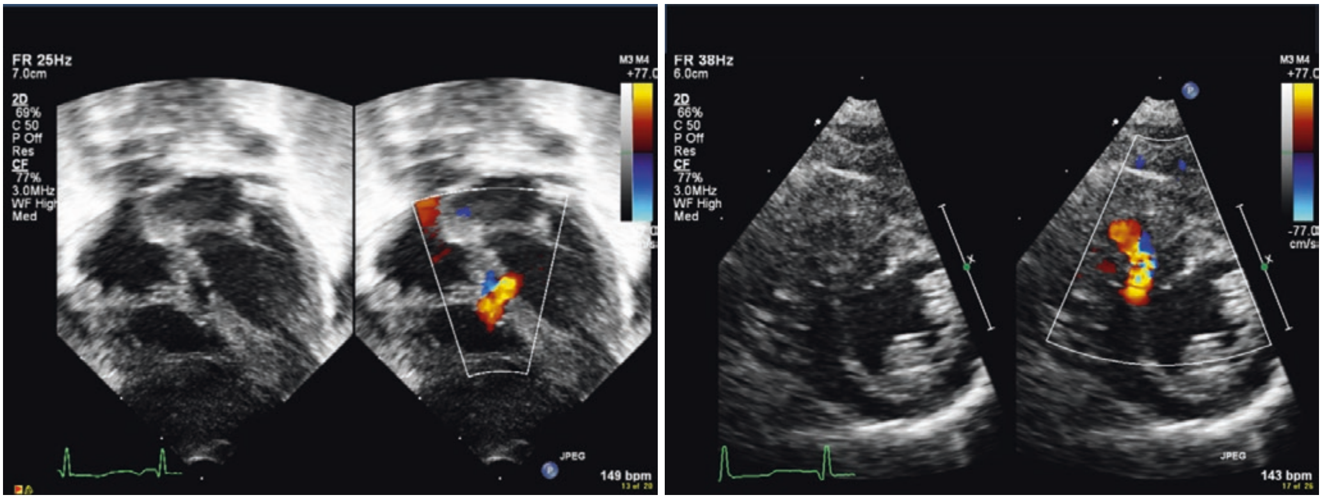
152 bpm

Fig. 93.6 Transthoracic echocardiographic image in the parasternal short axis demonstrating a doubly committed subarterial ventricular septal defect. There is fibrous continuity between the aortic and pulmonary valves seen in this defect


FR 25Hz
7.0cm
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69%
C 50
P Off
Res
CF
77%
3.0MHz
WF High
Med
+77.0
JPEG
149 bpm
FR 38Hz
6.0cm
2D
66%
C 50
P Off
Res
CF
77%
3.0MHz
WF High
Med
+77.0
-77.0
cm/s
JPEG
143 bpm

Fig. 93.7 Transthoracic echocardiographic images in the apical four chamber demonstrating a muscular ventricular septal defect. There is a defect in the muscular septum evident in the two dimensional image with left to right shunt seen on colour flow

Medical Management

For those patients with a small VSD, no treatment will be needed and over time some may close spontaneously. However, long term observation is recommended as some may go on to develop complications such as aortic valve regurgitation, double chambered right ventricle and sub aortic stenosis.

In patients with a haemodynamically significant VSD medical therapy is initiated to reduce symptoms and optimise weight gain prior to intervention. First line therapy should include diuretics such as the loop diuretic furosemide with or without potassium sparing diuretics such as spironolactone and amiloride. Angiotensin converting enzyme (ACE) inhibitors such as captopril are used in selected cases to reduce systemic afterload with the aim to reduce the left to right shunt. In parallel, nutrition should be optimised with support from dieticians and will include the use of high calorie feeds, and in some instances, nasogastric feeding. A small proportion of babies will fail to respond to medical therapy and require hospital admission. In those with significant respiratory compromise, non-invasive ventilation such as continuous positive pressure ventilation (CPAP) may be required along with consideration for early surgical intervention.

Indications for Intervention

Surgical intervention is indicated in haemodynamically significant VSDs. The timing of closure will be dependent on a number of variables such as the weight and clinical status of the patient, response to medical therapy, any associated medical conditions and clinical co-morbidities. Large defects will usually be closed surgically at approximately 4–6 months of age but may need to be closed earlier if the patient is symptomatic, failing to thrive and unresponsive to medical management.

Defects which are not amenable for primary repair such as in low weight infants, multiple muscular VSDs or defects below the moderator band may lead clinicians to consider performing a pulmonary artery band (PAB). Failure to intervene in haemodynamically significant defects risks the deleterious effects in the long term of pulmonary arterial hypertension.

Closure of VSDs in the Context of High Pulmonary Vascular Resistance

The presence of a VSD in a patient who has developed a high PVR poses significant challenges. Complete closure of such a defect can lead to acute RV failure. Echocardiography can be used to indirectly estimate the RV pressure and guide whether further investigation is required. The easiest method in the presence of a VSD to assess RV pressure is to measure the pressure gradient across the VSD by continuous wave Doppler and convert the velocity into pressure utilising the modified Bernoulli equation. Other methods to estimate RV pressure by echocardiography include peak TV regurgitation jet, evidence of flattening of the interventricular septum in systole and/or diastole, RV outflow Doppler acceleration time, early diastolic pulmonary regurgitation velocity, pulmonary artery diameter, right atrial area and inferior vena cava collapse on inspiration. Despite the multiple available methods of echocardiographic assessment, the gold standard for assessment of high pulmonary vascular disease and confirmation of a diagnosis of pulmonary hypertension is right heart cardiac catheterisation. Alongside diagnosis, right heart catheterisation can assess the severity of haemodynamic impairment and reversibility through vasoreactivity testing. Left heart catheterisation can be performed alongside this in the same procedure if required [12–14].

In patients where it is felt unsafe to completely close the defect, different surgical techniques have been developed to allow partial closure of the defect enabling the right ventricle to offload if needed. Options include unidirectional valved patches or a fenestrated patch [15–19].

Surgical Intervention

Standard Closure of Perimembranous VSD

The approach here described to close a perimembranous VSD is via the right atrium (RA) with a combination of continuous and interrupted sutures and a bovine pericardial patch.

The operation is performed via a midline sternotomy, partial or total thymectomy, followed by an inverted T perciardiotomy and its suspension. Suspending the pericardium on the right edge allows subsequent rotation of the heart towards the left chest so as to bring the RA anteriorly.

A patent ductus arteriosus (PDA), if present, is ligated at this stage. Cardiopulmonary Bypass (CPB) is achieved with direct bicaval cannulation with metal angled tip cannulas, and aortic return in the ascending aorta. Retraction manoeuvres to identify and cannulate the inferior vena cava (IVC), in smaller babies with overloaded heart, could compromise haemodynamic stability before CPB is established. In such cases we prefer to cannulate the superior vena cava (SVC) first and then dissect and cannulate the IVC on partial CPB, while ventilation is maintained. In severely dilated hearts, with a large distended right atrium, CPB is started with the IVC cannula in the RA appendage. This usually allows to achieve full CPB flow, to stop lung ventilation and cannulation of both caval veins (SVC first and then IVC with the same RA cannula) on an empty heart.

CPB is conducted at normothermia at 37 °C. After aortic cross clamping and during delivery of antegrade cold blood cardioplegia, a vent is usually inserted in the right superior pulmonary vein. With total CPB and caval vein isolation, the RA is opened in the midportion of the appendage, longitudinally to the atrioventricular groove and the incision extended inferiorly towards the IVC. Two 6-0 polypropylene sutures are positioned near the TV annulus at 10 o'clock and 2 o'clock and stayed back towards the assistant's side. The heart rotates in such way that the TV is fully into view (Fig. 93.8). Internal inspection of the heart is accomplished followed by inspection of the RV and of the VSD. In perimembranous VSD, the attachment of the septal leaflet of the TV is one of the VSD margins; hence it is sometimes useful to retract the leaflet to fully appreciate this margin. In particular the superior margin towards the aorta and inferiorly towards the inlet area where the conduction system runs. We find useful to position one or two horizontal mattress pledgeted sutures across the TV annuls so to retract and extrovert the septal leaflet of the TV. The pledgets will sit on the RA side, and these sutures could be later used to anchor the VSD patch on the TV margin (Fig. 93.9).

In most cases, there are TV chordae crossing the margins of the VSD, attaching either directly on the crest of the VSD or onto the interventricular septum via papillary muscles. Inspection of the VSD is performed, so to make sure all the

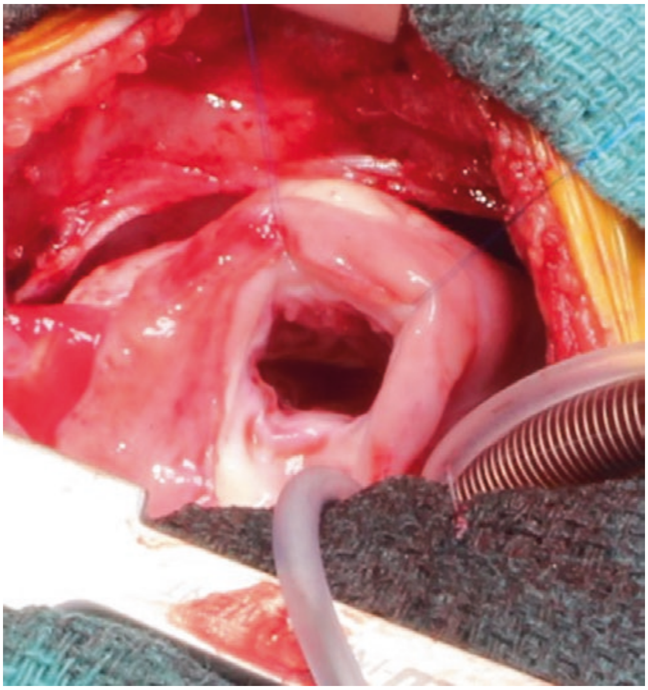

Fig. 93.8 Intraoperative picture showing the exposure of the right atrium and the tricuspid valve

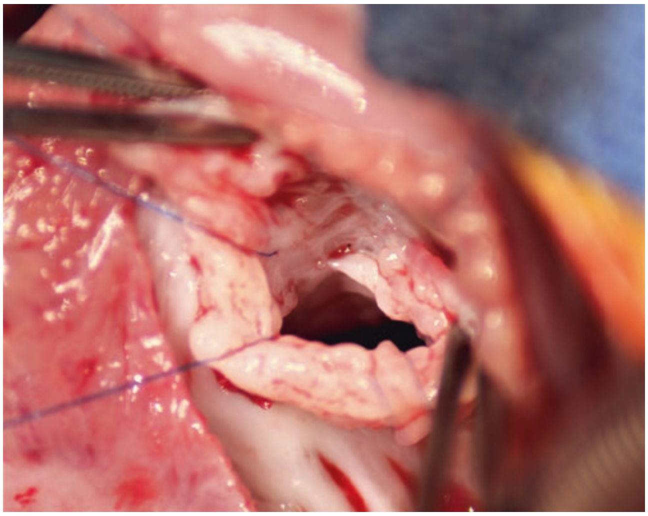

Fig. 93.9 Retraction with pledgeted sutures of the septal and anterosuperior tricuspid valve leaflets exposes the ventricular septal defect margins particularly the subaortic area

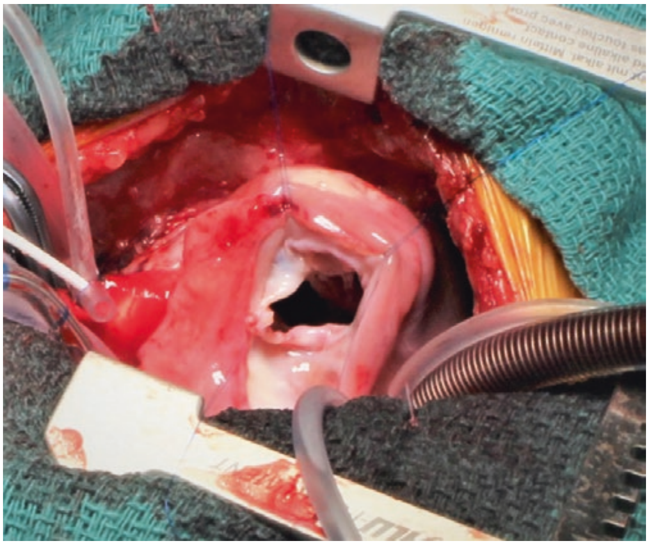

Fig. 93.10 The chordae from the medial papillary muscle partially obscure the inferior margin of the ventricular septal defect, and it has been detached and retracted

margins of the VSD can be seen and reached. It is important to ascertain if any chordae is going to obstruct the VSD patch placement, and if sutures can be passed around it without compromising the repair or damaging vital structures. Gentle traction of the anterosuperior leaflet with small right angled instruments helps exposing the rims, but short chordae could prevent to expose the VSD margins fully. In such cases, either partial TV leaflet detachment from the TV annulus, or chordae disconnection from the papillary muscle attachment should be considered to improve exposure (Fig. 93.10).

In perimembranous VSD, one margin of the VSD touches the central fibrous body which is the area of fibrous continuity of the membranous septum and the annuli of the tricuspid, mitral and aortic valves. In this case the anteroseptal commissure, with the medial papillary muscle, lays to the left of the conduction system.

In case of outlet perimembranous VSD, it is important to inspect the subaortic extension to appreciate the relationship of the AV apparatus (annulus and leaflets) with the VSD. In such cases we find useful to deliver cardioplegia for few seconds to fill the aortic root and inspect the relationships of the AV to the VSD.

In case of inlet extension of the perimembranous VSD, the defect extends towards the commissure between septal and posterior TV leaflet and the chordae supporting both leaflets attach to a papillary muscle from the posterior limb of the trabecular septomarginalis. Chordae crossing the defect could make it difficult to identify this margin which lays to the right of the defect (surgical view). In this case we recommend retraction by encircling the chordae with a thin thread or, in case of short and thick chordae, its detachment from the papillary muscle origin retracting backwards the RA (see below) so that the patch can take a wider pathway away from the muscular margin of the VSD covering the penetrating bundle of the conduction system (Fig. 93.10).

All the above information is used to shape the VSD patch. Patch material employed can be heterologous pericardium (porcine, bovine, equine), autologous pericardium if treated with glutaraldehyde, Goretex©, double velour Dacron or Collagen Bioscafold (CardioCel®). When cutting and shaping the patch, we keep in mind that the patch has to be bigger than the actual VSD, and the suture line will lie at least 2 mm away from the defect borders. In case of outlet extension, the shape of the patch needs to be wider so to accommodate the aortic valve apparatus. The inferior border of the patch, which will cover the area over the penetrating bundle, will have an extension to take a larger route away from the corner between the septal leaflet of the TV and the inferior border of the VSD.

The patch is positioned over the defect to confirm the size, and trim it accordingly. We position the patch over the right sternal edge drapes held in place with a mosquito. As a general rule we use double-ended polypropylene pledgeted suture with a half circle needle. For babies below 6 kg, a 6-0 thread with a 10 mm needle is used, where for bigger babies, a 5-0 thread with 10 mm needle is employed. It is important to remember that the endocardium of the heart is the strongest layer of the muscle, holding the suture in place. Therefore, attention is given not to weaken the endocardial layer. The first sutures are horizontal matters at 12 o'clock deeply positioned into the trabecula septomarginalis with both needles, and passed onto the patch in the corresponding position (Fig. 93.11). The patch is then lowered down and the suture tied. The continuous suture line is conducted firstly superiorly towards the left; hence the first suture is into the patch (from the RV facing to the LV facing side of the patch), and gently pulled to retract the patch and expose the VSD margin. Then the needle enters into the muscle near the edge of the VSD and exits about 2 mm away into the RV side (Fig. 93.12). The suture line is continued in the same way, first in the patch and then in the muscle. Once the area near the AV is reached, if the muscular rim between the TV annulus and the VSD is thin, sutures could be placed tangentially till the commissure between anterosuperior and septal TV leaflets is reached. The suture is brought out on the TV annulus on the right atrial side and placed on a rubber shod.

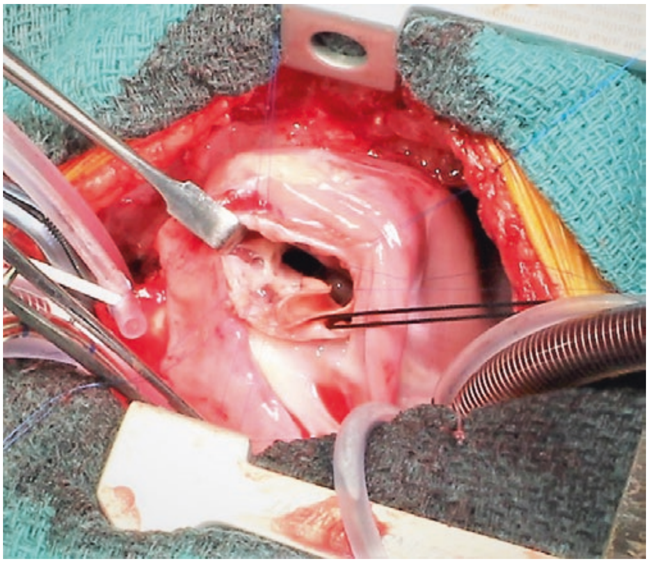

Fig. 93.11 The suture line starts at 12 o'clock

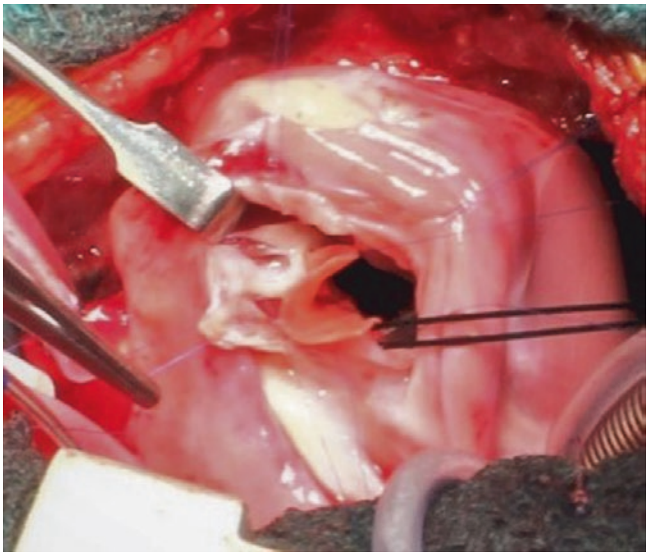

Fig. 93.12 The suture line continues upwards

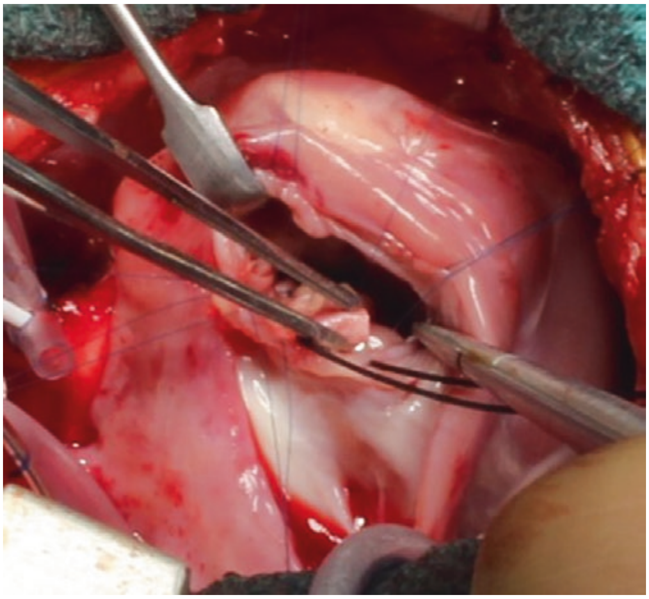

Fig. 93.13 The sutureline continues on the inferior border away from the edge of the ventricular septal defect so to reduce the risk of damaging the conduction system

The suture line restarts from 12 o'clock with the first 2–3 sutures again positioned deeply in the muscle and then in the patch. As the area of the penetrating bundle is approached on the right hand side, the sutures are positioned further away from the VSD margin, shallower but with longer strokes into the muscle, so to avoid the conduction tissue, but still offering enough muscle tissue to hold the suture line (Fig. 93.13). Once the TV annulus is reached the suture is brought on the RA side. Next is anchoring the patch to the septal leaflet of

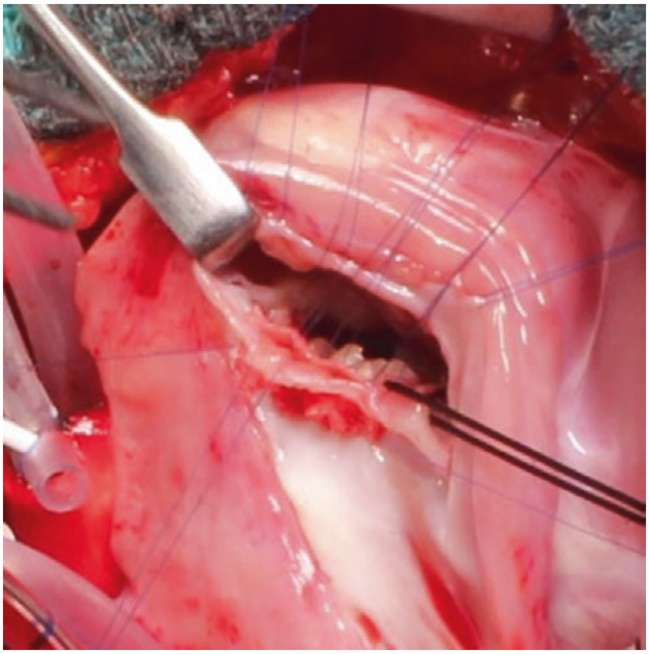

Fig. 93.14 Interrupted horizontal mattress sutures with pledgets are passed just across the TV annulus and then on the patch edge

the TV. The previously positioned sutures to retract the TV leaflet can be passed on the patch edge, and few more similar sutures are added if needed to cover the whole edge of the patch (Fig. 93.14). These sutures are tied and the two more distal are passed through the patch and the TV annulus exiting on the RA side and tied to the continuous suture line ends (Fig. 93.14). Careful inspection of the suture line is than accomplished and any area of possible residual VSD is secured with further horizontal mattress sutures.

If a TV chordae or leaflet was detached, after having reattached it in the corresponding area, the valve is tested under pressure by temporarily occluding the pulmonary trunk and injecting saline into the RV to ascertain TV competency (Figs. 93.15 and 93.16).

We prefer to directly close a PFO, if present, and then close the atriotomy while the cross clamp is still applied, to reduce the risk of air embolization in case of residual or additional unrecognised intracardiac communications.

Continuous Versus Interrupted Sutures

The interrupted sutures technique could be employed to secure the patch with the same carefulness for specific risky areas as described above. In this case a series of pledgeted sutures are first passed around the VSD margins and used to expose the more cephalad margins on the defect till the central fibrous body is reached. Next the sutures for septal leaflet of the TV are passed, leaving the pledgets to the RA side, followed by positioning of sutures towards the inlet area till the TV annulus is reached well away from the penetrating bundle. Each suture is than passed on the edge of a VSD patch previously trimmed to size to cover the VSD with a 2–3 mm margin and lowered down. Care is particularly taken not to exert too much traction while lowering the patch down and then the sutures are tied down.

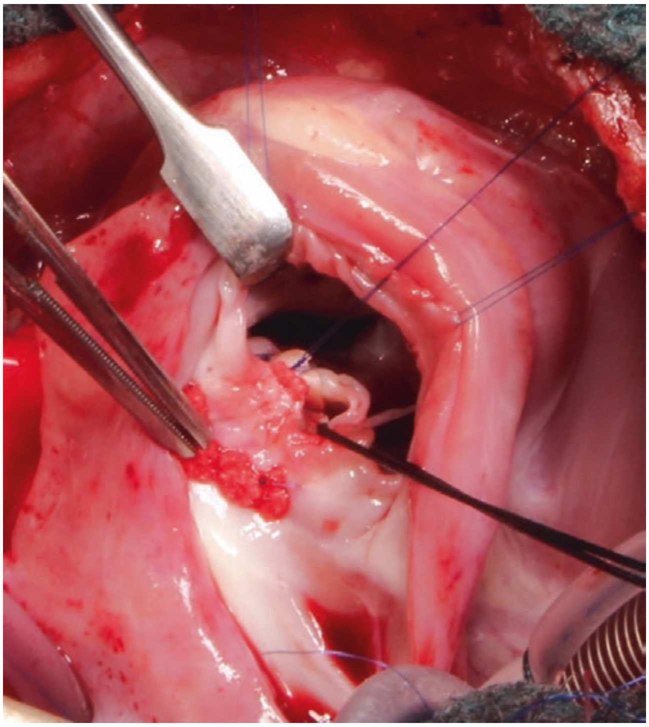

Fig. 93.15 The tricuspid valve chordae is reattached onto the patch with a plegeted suture. The forceps is holding the pledgets on the right atrial side with the patch held over the tricuspid valve margin

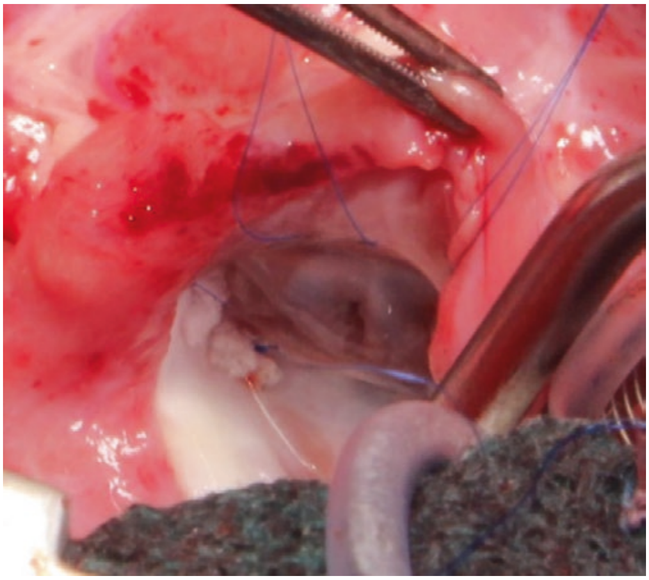

Fig. 93.16 Saline pressure testing of the tricuspid valve shows a competent valve

Doubly Committed VSD

In case of a doubly committed VSD, the approach is from either the main pulmonary artery (MPA) or from the aorta, according to the position of the VSD in relation to the great arteries. The majority of the time a fibrous continuity between AV and pulmonary valve (PV) is seen.

Subpulmonary: the incision is made transversally on the MPA just above the top of the commissures. The VSD is exposed by gentle PV leaflet retraction. The patch is shaped as a shield, to accommodate the curvature of the PV cusps within two commissures. The patch can be sutured to the muscular component with either a continuous or interrupted suturing technique. We anchor the superior edge of the patch to the posterior PV cusps with interrupted mattress pledgeted sutures, leaving the pledgets on the pulmonary sides.

Subaortic: in older children the VSD might be best approached via the AV, so the incision in the aorta is made transversally above the sinotubular junction, the incision is then extended towards the midportion of the noncoronary sinus. Retraction sutures are positioned and the VSD is inspected and the defect closed with a patch with a similar technique to the subpulmonary approach. Care is taken to identify the right coronary artery so that the sutures are position away from the orifice.

Muscular VSDs

Muscular VSDs proximal to the moderator band can be closed via the RA. The defect is surrounded by muscles, but identification of the margins could be difficult for the presence of muscular trabeculae, which at times need to be divided to fully expose the VSD rims. The defect is closed with a patch either with interrupted or continuous suture line with or without pledgets.

In case the defect lies below the moderator band towards the apex of the heart, it could be difficult to close it from the RA hence, if the patient is of a suitable size, a left or right apical ventriculotomy is employed. Usually the defect has multiple opening on the RV side, but one exit when seen from the LV apex. Approach from either LV or RV apex ventriculotomy has been successfully used [20, 21]. In case of significant apical VSD (single or multiple), we prefer to palliate with a PAB to allow growth of the child while protecting the pulmonary bed from deleterious effects of pulmonary over circulation. When the child's growth is suitable, we close the defect with a patch from a right apical ventriculotomy, dividing some of the trabeculae to fully appreciate the defect margins [22].

Special Circumstances

TV Apparatus Detachment

As mentioned above, at times the presence of thick TV chordae makes the inspection of the VSD rims difficult and the subsequent defect closure challenging, risking leaving a residual shunt around the chordae. Moreover, in case of outlet extension, exerting too much traction on the anterior TV leaflet might risk damaging the AV-TV leaflet continuity or, in case of inlet extension, running the suture line too close to the penetrating bundle [23]. In such cases detachment of the TV leaflet from the annular side make possible visualization of the VSD and its closure safer. When choosing the incision, it is important to leave a 2 mm area on both margins so to have enough tissue to anchor the VSD patch close to the annulus, and reattach the leaflet with a continuous suture. Long term follow-up has shown good results with no increase of tricuspid regurgitation [24].

In case of thick and short chordae crossing the VSD margin, we have adopted a different approach by detaching the chordae from its septal attachment and flipping it over to expose the area underneath the TV leaflet (Figs. 93.10 and 93.17). After the patch has been anchored to the TV annulus, taking a wider route away from the penetrating bundle, the chordae is reattached either to the muscle or to the corresponding area onto the patch with a pledgeted suture [25]. We believe that this technique offers a better visualization of the area around the penetrating bundle, allowing a more rightward positioning of the patch and reducing the incidence of heart block and right bundle branch block (RBBB).

Aortic Insufficiency

When perimembranous VSD has an outlet extension, if aortic regurgitation is present it needs to be addressed at the time of VSD closure. For the vast majority of cases the right AV cusp

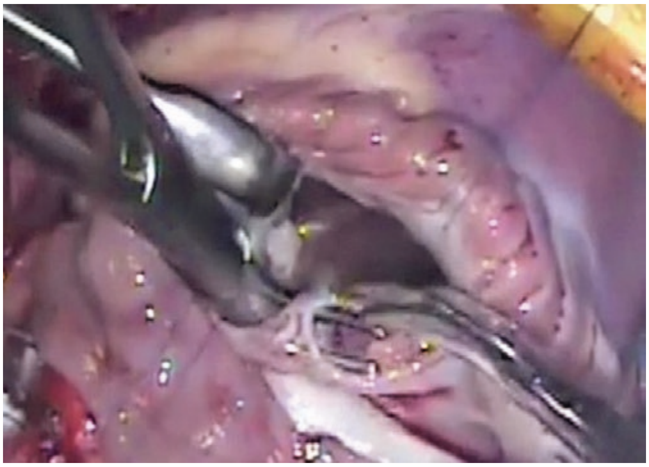

Fig. 93.17 Thick and short chordae can be detached to fully expose the ventricular septal defect margin

is usually redundant as it is dragged into the subaortic defect. In case of restrictive VSD, the AV cusp is sucked into the VSD by a Venturi effect, by the blood crossing the defect at high velocity [26]. In this case, we prefer closure of the VSD with a standard technique from the RA, followed by AV repair by means of resuspension of commissures via the aortic root.

In case of larger defect, the VSD is better closed with dual approach via both RA and aortic root, so to close the defect under the TV from the RA, but approaching the higher portion of the VSD as per a doubly committed VSD. In this case too, the AV needs repairing, most of the time by placating the redundant leaflet at the commissure, or by a small triangular resection of the excess leaflet [27].

Residual or Additional VSD

All patients having a VSD closed surgically undergo intraoperative echocardiogram on table and any residual VSD is usually picked up at this time. Most of these are small restrictive VSDs when smaller than 2 mm have been shown to close spontaneously with time [28]. In case of larger residual VSD (>3–4 mm), on table calculation of shunt fraction by Qp/Qs is performed and, if it is more than 1.5:1.0, a return on CPB and reoperation is performed to close the residual defect as it has been proven that these tend not to close spontaneously [29]. Occasionally the presence of additional undiagnosed VSD is made once the larger defect is closed. In such cases, return to CPB and closure of the additional defect is accomplished.

Pulmonary Artery Banding

In the context of isolated VSD, the role of PAB is nowadays limited to patients with low weight or with large apical VSD, or if a contraindication to the use of CPB is present.

We tend to perform PAB via median sternotomy with a Gore-Tex strip, 1 mm thick and 3–4 mm wide, passed around the pulmonary trunk. Tightening is performed according to the Trusler formula of 20 mm + kg weight in mm [30]. The optimal tightening is confirmed by increasing of systemic pressures, reduction of distal PA pressure close to 30 mmHg in systole, and peripheral saturation of 80–85% on 0.5 FiO_2. After PDA ligation, if present, the band is passed around the proximal pulmonary trunk just above the PV commisures but below the PA branches origin. It is progressively tightened to the desired markings by Ligaclips placement. When the optimal haemodynamics and respiratory conditions are met, a suture is passed across the PAB and the lateral edges are fixed to the pulmonary artery wall with further suturing. In cases of haemodynamically and respiratory unstable patients, we have favoured a staged approach. We tighten the PAB as much as allowed without compromising the haemodynamics, leaving the sternum open with the chest wound covered with silastic membrane. Retightening towards the desired values is performed in pediatric intensive care unit over the next 24–48 h.

New Approaches

In recent years a different approach via a right axillary incision has been proposed, offering a cosmetically superior result than a median sternotomy. The technique needs a learning curve of approaching the mediastinum and its structures from this limited view. Nonetheless long term results comparing this approach to the standard one are needed [31].

Hybrid Approach to VSD Closure

The hybrid approach encompasses both a surgical and catheter intervention to close mainly muscular or apical VSDs. It was first performed in a human infant in 1998 [32, 33]. This method of VSD closure is advantageous in selected patients as it is less invasive, avoids the need for CPB in most cases and allows for a short duration of inpatient admission.

After median sternotomy and pericardiotomy are performed, a purse string suture is applied to the RV free wall. Under TOE or fluoroscopy screen, a needle is placed through the purse string and a short vascular sheath is then inserted via Seldinger's technique over a wire across the VSD. The device is then deployed over the delivery sheath and when suitable position is confirmed, the sheath is removed and purse string suture tied. Advantages of this technique are the avoidance of CPB and the potentially deleterious effect of a ventriculotomy.

Multicentre studies have shown high levels of procedural success in selected group of patients but not a widespread adoption. One multicentre study over a 10 year period of 47 patients showed good outcomes with significant complications in two patients (surgical repositioning of the device and ventricular pseudoaneurysm). Mid-term follow up in this study showed residual shunt in two patients and no AV regurgitation or impairment in ventricular function in the remaining patients [34].

Non-surgical Intervention

Transcatheter Device Closure of Muscular VSDs

Percutaneous device closure of muscular VSDs was initially described in 1988 [35] with numerous modifications of both technique and equipment. Advantages of device closure include avoidance of CPB and faster recovery. The transcatheter approach can be used for both muscular and perimembranous VSDs with similar techniques. Perimembranous VSDs are usually closed from the left ventricular side of the defect. The device is delivered over a guide wire loop via a delivery sheath from the femoral vein. Muscular outlet defects are also usually closed via a femoral approach with apical defects best approached from the jugular vein.

Percutaneous closure is usually reserved for larger children as the size of the sheath may lead to vascular damage in smaller patients. In selected patients, outcomes are comparable to surgical results particularly in terms of complications and residual shunt. Longer term studies are needed to provide clearer evidence when results are compared with operative intervention [2, 3, 36–39]. Late complete heart block has been reported in device closure of perimembranous VSD due to the proximity to the conduction system.

Pacemaker Implantation After VSD Closure

Complete heart block is a rare complication of closure of an isolated VSD. Large series of patients have been studied and the overall incidence of pacemaker implantation remains low, below 1%. Given the proximity of the conduction tissue to some defects, meticulous technique, as described above should reduce the risk of this complication. Defects at particular risk include perimembraous defects and juxta-arterial defects with perimembranous extension.

Late Effects of Surgical Closure of Isolated VSD

Up to 20 years follow up data is available for closure of isolated VSD. The overall results show that patients operated on in early life have normal exercise capacity when tested with a modified Bruce protocol [40–42]. Nonetheless, evolving evidence utilising measurements of peak oxygen consumption uptake and aerobic capacity have shown, in small groups of patients, poorer results in operated patients when compared to controls [43, 44].

Imaging studies assessing cardiac function have found subtle changes in cardiac structure and function. Echocardiography and cardiac magnetic resonance imaging studies assessing patients up to 20 years post intervention have shown evidence of RV dilatation and increased RV end diastolic dimension with lower RV fractional area change and increased radial strain [45, 46].

Newer imaging studies are assessing the force frequency relationship on myocardial performance using exercise and echocardiography. These studies have shown alterations in both left and particularly right ventricular function in patients with previous isolated VSD closure. Given the longevity and long-term health of these patients the impact of degenerative cardiac disease will be important to assess over time.

Conclusion

Isolated VSD is the most common congenital cardiac anomaly in children. An abnormal communication between the right and left ventricles with shunt formation is the main mechanism of hemodynamic compromise in VSD. While many VSDs close spontaneously, if they do not, large defects can lead to detrimental complications such as pulmonary arterial hypertension, ventricular dysfunction and an increased risk of arrhythmias. Surgical closure remains the standard of care with transcatheter closure emerging as a promising alternative.

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Patent Ductus Arteriosus

Robroy H. MacIver

High Yield Facts

- The ductus arteriosus arises from the sixth branchial arch.
- Spontaneous closure after 1 year of age is rare.
- Closure either by medical or surgical means in preterm neonates remains controversial.
- Surgical ligation of the ductus has a low morbidity and mortality rate.
- Device closure of the ductus in neonates <3 kg is less common secondary to peripheral vascular access limitations and size of devices.
- Long term results of open surgcal duct ligation are excellent with ligation rates over 95% in most series.

Introduction

The patent ductus arteriosus is an anatomical bridge between neonatal and fetal circulation. It was one of the first congenital cardiac defects to be surgically treated in 1938 by Robert E. Gross [1]. Additionally, the artificial maintenance of the ductus arteriosus by medical means has allowed for much of the elective neonatal congenital surgery now performed. Conventional palliation of congenital heart defects now includes endovascular stenting of the ductus to maintain patency. Incidence rates of patent ductus arteriosus in children carried to term are between 1 in 500–2000 births depending on method of surveillance [2, 3] favoring females over males. This chapter will review the natural history and management, both medical and surgical, of the patent ductus arteriosus.

Embryology and Anatomy

The ductus is formed from the sixth aortic arch, most commonly the left, and therefore anatomically follows the development of the pulmonary artery. The wall of the ductus arteriosus is composed of mainly muscular tissue versus the elastic layers of the pulmonary and aortic walls. The preponderance of muscular tissue allows for the future two stage closure of the ductus by constriction of muscular cells followed by proliferation of fibroblasts. Abnormal migration of ductal tissue cells onto adjoining vessels may contribute to coarctation of the aorta and/or pulmonary artery. As the sixth aortic arch initially develops in the neck (branchial arch), the recurrent laryngeal nerve becomes intimately involved around the ductus, and is brought down into the chest during development. The recurrent laryngeal nerve has multiple branches that fan out after origin from the vagus. The ductus arteriosus normally courses from the left/main pulmonary arterial junction to the anterolateral aspect of the aortic arch distal to the takeoff of the left subclavian artery. Prior to post-natal constriction of the ductus, the diameter is often equal to that of the descending aorta.

Variation of embryonic branchial arch regression leads to aortic arch abnormalities. These abnormalities subsequently cause variations in location of both the recurrent laryngeal nerve and ductus. The paths of the recurrent nerves will follow the sixth branchial arch and therefore will be on the right if the sixth branchial arch on the right does not regress, or follow the fourth (right subclavian artery or aortic arch) if both the fifth and sixth arch regress. Non regression of the fifth arch is rare. Due to the embryonic origin of the ductus and recurrent nerve, it is important to note that they will always be anterior to the esophagus.

Normal Physiologic Postnatal Closure

PGE2 and PGI2 circulating while in utero maintain vasodilation of the ductal tissue via prostanoid receptors [4]. Immediately with the onset of respirations and separation

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from the placenta, hormonal and elevated oxygenation levels cause constriction of the muscular tissue of the ductus. PGE2 and PGI2 are subsequently metabolized in the lungs after birth. In full term infants the ductus is obliterated in the first 2–4 days after birth.

In some congenital heart syndromes such as tetralogy of Fallot with absent valve and truncus arteriosus the ductus closes in utero. Alternatively, external factors such as Rubella infection of the mother can lead to a higher incidence of PDA [5, 6]. As fetal surgery becomes more routine, manipulation of the ductal physiology may extend from the post-natal into the in-utero management.

Patency with Pulmonary Overcirculation

Children with patent ductus arteriosus, as their pulmonary resistance naturally falls, have a "left to right" shunt. The quantity of flow depends on both the size of the ductus, and the resistance of the pulmonary arterial bed either by microcirculation or poor development of the main branch pulmonary arteries. The perfusion of the brain and viscera are decreased due to diastolic run off. There is also some evidence that brain development is affected by prolonged ductal flow, although clinical correlation is lacking [7].

Symptoms of poor feeding tolerance and increased pulmonary work are common in neonates with PDA. Most commonly this presents as an inability to wean from positive pressure ventilator support. The clinical picture of inability to wean off positive pressure support is often clouded by poorly matured lung tissue in premature children. Older children with overcirculation are usually asymptomatic with discovery of the shunt either through a murmur or incidentally on imaging. Class 1 indications for closure of the ductus in the setting of overcirculation are [8]:

1. Left atrial and/or left ventricle enlargement or if pulmonary arterial hypertension is present, or in the presence of net left to right shunting.
2. Prior episode of endarteritis.

Age at presentation is important when considering implications of closure. The literature focuses on premature children, and the benefit on pulmonary and visceral maturation gained with ligation of patent ductus at a young age versus watchful waiting. From that discussion, there have been trials of prophylactic treatment of patent ductus arteriosus in the setting of extreme low birth weight with mixed results [9, 10]. Medical treatment utilizing down regulation of PGE receptors has shifted gradually from the use of indomethacin to ibuprofen to acetaminophen in an attempt to decrease complications of necrotizing enterocolitis and intracranial bleeding [11].

Patency Without Overcirculation

Treatments of patent ductus arteriosus without overcirculation are changing. The majority of these patients are asymptomatic, and the lesion is often found either on follow up testing after prematurity, or incidentally with more accurate and widely used diagnostic tests. Past recommendations were for closure only if a murmur was audible. The variability of this method along with improved morbidity rates with the use of catheter based therapies have led to indications moving towards closure if seen on echocardiography. The incidence and natural history of endarteritis has also improved incrementally likely secondary to better dental treatments and increased use of prophylactic antibiotics [12].

Open Surgical Methods of Closure

For a congenital heart surgeon anatomical encounters with the patent ductus arteriosus are usually in the setting of ligation. Although ligation is a technically clear endpoint, pitfalls in ligation can lead to major complications. Identification of key structures is the main strategy in avoidance of surgical misadventure. Preoperatively determining sidedness of the arch by echocardiogram is important in determining the correct side for thoracotomy. Also, on the echocardiogram flow should be either "left to right" or bidirectional.

A posterior serratus sparing thoracotomy at the third or fourth intercostal space is ideal for locating the ductus. Many groups will do this procedure in the neonatal intensive care unit (NICU). Important aspects of going forward with this strategy are adequate lighting, access to blood products and a dedicated supporting structure. Moving the child to the operating room is ideal from a technician standpoint, but care must be made to assure airway patency and body temperature of the premature infant. The surgeon must determine if they are comfortable with jet ventilation strategies and coordinate this with the NICU and anesthesia teams preoperatively. Intravenous access depends on the level of care being given, but as a baseline there should be enough access to give a large volume of fluid quickly in the event of ductal rupture. Blood products should be in the room. Often the child will not tolerate the lung being compressed for long periods of time which will need to be anticipated and frequent breaks in retraction must be allowed.

Intraoperatively identification of the following structures is a must prior to ligation: the transverse aortic arch, the left or right subclavian artery, the ductus, and the descending aorta. Use of the crossing vein over the aorta is useful in initial identification of a ductus that is covered in lymphatic tissue, but is by no means a singular identifier in ligation. Often lymphatics will need to be clipped in an effort to avoid long term lymphatic drainage.

Once the ductus is identified use of blunt and sharp dissection in the plane around the ductus is preferred versus electrocautery in an effort to avoid damage to the recurrent laryngeal nerve. A right angle type dissection at the superior margin should be used with care as the ductus and transverse aorta are intimate and the junction can be quite friable. Approaching the superior junction with a direction posterior and inferior while the child is in a decubitus position can aid in avoiding puncture wounds to the transverse aorta. Dissection at the inferior margin should be made with clear identification of the ductal wall as the nerve can get bundled with surrounding connective tissue and incorporated into the tie or clip.

Ligation can be approached by either a clip or tie. In large ducts, with a concern for re-cannulation, ligation and division is an alternative, but specialized clamps should be used (ductal clamps) that will not slip off while dividing a relatively short vessel. Control of the proximal and distal aorta should be acquired prior to ligating a short and broad ductus. Clamping similar to that done in end to end coarctation repair is useful, but must be communicated to the anesthesiologist as blood pressure management during this time will be active.

Pitfalls can occur both from derivations of anatomy and physiology. Identification of the ductus can be confused in the case of a narrow aortic isthmus. The narrow isthmus can be misidentified as the subclavian artery if the transverse arch is covered by fat or lymphatic tissue. This error will lead to the ductus being identified as the transverse arch, with the left pulmonary artery as the “ductus”.

High pulmonary artery pressures post ligation can lead to right heart failure. It is not uncommon to need the addition of dopamine or epinephrine for the first 24 h postoperatively. More acute hemodynamic changes after ligation must make the operator reconsider anatomy such as ligation of the transverse aortic arch, distal aortic arch or the presence of structural cardiac disease. Coronary arteries off the pulmonary artery have been described as presenting in the setting of duct ligation as acute fibrillation or decreased cardiac output after ligation. Swift diagnosis and attempts at reversal of ligation and/or mechanical support are most appropriate in these settings.

A video assisted thoractomy (VATS) approach is possible for ligation in larger neonates. Although there was initial enthusiasm for this approach, the ability to close the ductus with a catheter based device in this same age group has decreased the amount of surgeons who offer this approach. It will be difficult to amass enough patients to show statistical significance of this approach versus an open thoractomy due to the excellent outcomes in both.

Long term results of open surgical duct ligation are excellent with ligation rates over 95% in most series. Rates of recurrent laryngeal nerve injury vary widely depending on follow up methodology used [13]. Scoliosis rates are increased after an infant has a thoracotomy [14]. Follow up after ligation should include an echocardiogram to verify normalization of pulmonary artery pressures [8].

Catheter Methods of Closure

The most significant change in the management of patent ductus arteriosus in the last 40 years has been the progression of catheter based therapies. The first report of a ductus being occluded in the literature was in 1967 [15]. The initial devices were designed as a plug taking advantage of two common aspects of patent ductus arteriosus in older children; a large pressure gradient between the right and left circulations, and a funnel or cone shaped ductus [15]. More widespread application of this technique has led to more specialized devices for ductal occlusion including specifically shaped coils and devices. Specialized devices have allowed for closure in smaller patients. Currently coils are the main treatment strategy. Other device examples are the Amplatzer duct occluder, Amplatzer vascular plug II, Gianturco-Grifka sack, and Amplatzer muscular VSD device. More recently premature infants have been able to be treated by device closure. Although the majority of this population is still being treated by surgical means, success rates have improved with low conversion rates to surgical closure [16].

Closure rates for catheter based devices are between 90% and 100% [12]. The majority of complications with device closure are either secondary to device embolization or peripheral vascular injury from access. Other less frequent complications include decreased flow to the branch pulmonary artery or descending aorta after device deployment. Future devices with smaller vascular sheath sizes may allow for the techniques to be used in neonates on a more routine basis.

Conclusion

Patent ductus arteriosus is now easily identified and delineated with contemporary imaging techniques. Treatments of patent ductus arteriosus are effective and diverse. As the methodologies continue to evolve, care should be given to identifying individual institutional capabilities before committing to a strategy. In the end, obliteration of the ductus with a minimization of mortality and morbidity is the goal.

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Aortopulmonary Window

95

G. Deepak Gowda and B. C. Hamsini

High Yield Facts

- Aortopulmonary window (APW) is a rare, surgically correctable congenital cardiac anomaly representing 0.2–0.3% of all congenital cardiac lesions.
- Echocardiography is generally diagnostic and has replaced angiography as the gold standard.
- Patients typically present with symptoms of congestive heart failure (tachypnea, diaphoresis, failure to thrive, or recurrent respiratory infections).
- Operative treatment is indicated as soon as the diagnosis is established, regardless of the patient's age.
- Unless there is a right-to-left shunt despite oxygen administration, no patients with APW should be denied the operation.
- Elective repair is advised before age 3 months.
- Long-term outcome after operative correction is excellent regardless of age or pulmonary vascular resistance.

Introduction

The aortopulmonary window (APW) is a communication between the ascending aorta and the pulmonary trunk and/or right pulmonary branch, in the presence of both separate sigmoid valve planes, which differentiates it from truncus arteriosus (TA). APW is a rare, surgically correctable congenital cardiac anomaly. This lesion represents between 0.2% and 0.3% of all congenital cardiac lesions [1, 2]. It was first described by Eliotson in a clinicopathologic discussion given at St. Thomas' Hospital in London in 1830 [3]. Dodds and Hoyle gave the first clinical diagnosis in 1949 [4]. Gross did first successful ligation in 1952 [5]. Subsequent classification was done by Mori et al. in 1978 [6] and by Richardson and associates in 1979 [7]. This lesion is associated with rapid progression of pulmonary arterial hypertension (PAH) unless it is corrected surgically.

Embryology

The beginning of the formation of the aortopulmonary septum can be traced to the fifth week of development, when pairs of opposing ridges appear in the truncus, called cushions or truncus swellings. They grow towards the aortic sac, twisting counterclockwise around each other, foreshadowing the spiral course of the future septum [8]. After complete fusion, the ridges form the aortopulmonary septum, dividing the truncus into separate aortic and pulmonary channels. Neural crest cells migrate to the outflow region of the heart contributing to the formation of the aortopulmonary septum. There are many proposed mechanisms explaining outflow tract defects, including direct insults to the truncus swellings, insults to neural crest cells that disrupt signaling to truncus swellings or insults to neural crest cells that disrupt their contribution to fusion. All proposed mechanisms can potentially disrupt the whole process of outflow tract formation. Abnormalities in neural crest migration and signaling are linked to velocardiofacial syndrome, because neural crest cells also contribute to the craniofacial development. Unlike other conotruncal malformations, such as truncus arteriosus or interrupted aortic arch (IAA), the risk of associated chromosomal abnormalities in APW, including 22q11 deletion, seems low [2].

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Classification

Several classifications have been proposed for APW. The most often used is that of Mori et al. [6], which divides it into type I, or proximal (70%) (the defect is circular, located in a zone equidistant between the sigmoid valve plane and the pulmonary bifurcation); type II, or distal (25%) (of spiral form, it affects the trunk and origin of the right pulmonary artery), and type III (5%) (complete defect of the aortopulmonary septum).

Ho and associates [9] modified this classification in a way that is more useful to interventional cardiologists considering transcatheter device closure of APW. They keep the basic terminology from Mori and associates as defined above but add additional description. Proximal defects are noted to have little inferior rim separating the APW from the semilunar valves. Distal defects are noted to have a well-formed inferior rim but little superior rim. Total defects are called confluent defects with little superior and inferior rims. Finally, intermediate defects are defects with adequate superior and inferior rims; this type is obviously the group most suited for device closure.

Classification of APW as proposed by Richardson et al. [7] includes (A) Type I is a "typical" APW between the posteromedial wall of the ascending aorta and the main pulmonary artery. (B) Type II is located between the posterior wall of the ascending aorta and the origin of the right pulmonary artery. (C) Type III defects are defined as an anomalous origin of the right pulmonary artery from the posterolateral wall of the ascending aorta.

Classification of APW used by the Society of Thoracic Surgeons [10] includes (A) Type I—proximal defect; (B) Type II—distal defect; (C) Type III—total defect; and (D) Type IV—intermediate defect (as described by Ho et al. [9]). In proximal extension of the APW, the ostium of the right coronary artery may come from the APW or originate in close proximity to it.

Associated Conditions

APW can be associated with other congenital cardiac defects in 25–65% of cases. The associated conditions include patent ductus arteriosus (PDA), left superior vena cava, right aortic arch, ventricular septal defect (VSD), patent foramen ovale (PFO), supramitral ring, mitral regurgitation and interrupted aortic arch (IAA) mostly type A [11]. As reported by Braunlin and coworkers IAA is associated with 43% of cases of APW and coarctation of aorta in 14% cases [12]. Sometimes APW can be associated with tetralogy of fallot and anomalous origin of coronary artery. Anomalous origin of right pulmonary artery from ascending aorta is a rare congenital lesion with a high mortality and morbidity. The natural history of this lesion is that of progressive heart failure with a 70% mortality rate at 1 year compared with an 84% survival rate at 1 year with surgical repair. The combination of an APW, aortic origin of the right pulmonary artery, intact ventricular septum, and interruption or coarctation of the aortic arch is termed the *Berry syndrome*.

Pathophysiology

The lesion, if large, resembles a large PDA. When pulmonary vascular resistance (PVR) falls the patient develops severe congestive heart failure that often causes early death. If they survive, pulmonary vascular disease occurs [13–15]. Occasionally, if the window is small or there is stenosis of one or both pulmonary arteries, neither heart failure nor pulmonary vascular disease occurs. Under 1 year of age there is usually a large left-to-right shunt and pulmonary and aortic systolic pressures are equal or almost equal, but PVR is usually but not always near normal [14]. In older children pulmonary hypertension is still present, but shunts vary in size, depending on PVR. This lesion resembles a large ventricular septal defect in the time course of pulmonary vascular disease.

Clinical Features

Clinical manifestations in patients with an aortopulmonary window depend on the size of the defect and associated cardiac anomalies.

Symptoms

Patients typically present with symptoms of congestive heart failure (tachypnea, diaphoresis, failure to thrive, or recurrent respiratory infections).

Signs

On examination, the left precordium is prominent because of marked cardiomegaly. Loud continuous murmur with systolic accentuation which is heard best at the left upper sternal border. The second heart sound may be accentuated and narrowly split. In a large shunt, the diastolic blood pressure is usually reduced, with a concomitant widened pulse pressure and, on occasion, a water-hammer pulse may be present.

Diagnosis

Chest radiograph and electrocardiogram (ECG) show evidence of left and right ventricular enlargement and increased pulmonary blood flow. Left atrial enlargement as a result of increased pulmonary blood flow is usually prominent. Echocardiography (Fig. 95.1) is generally diagnostic and has

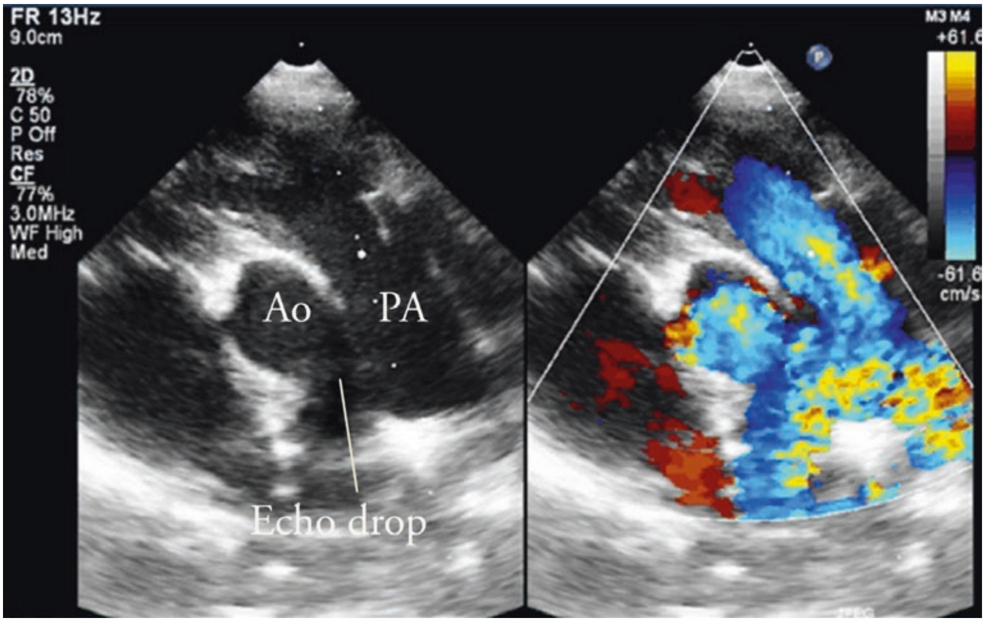

Fig. 95.1 2D echocardiography in modified short axis view shows echo dropout between aorta and pulmonary artery. *Ao* aorta, *PA* pulmonary artery

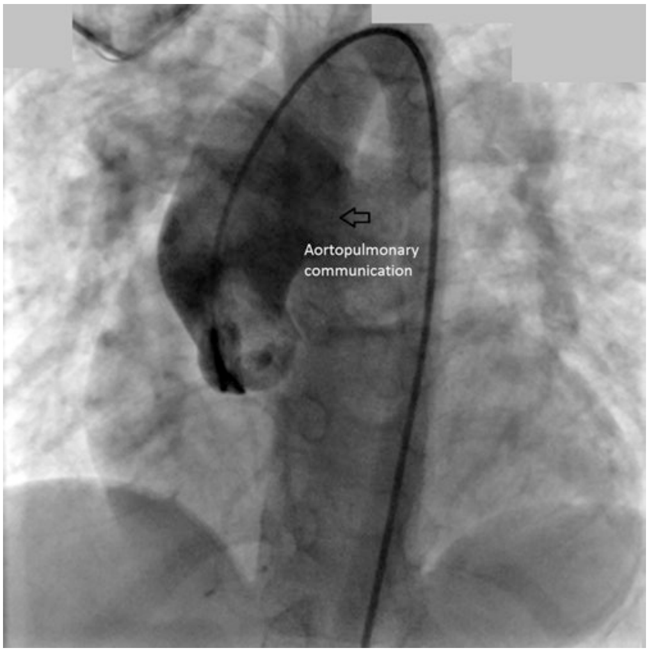

Fig. 95.2 Catheterization study (catheter course from descending aorta to arch and ascending aorta) showing aortopulmonary communication

replaced angiography as the gold standard [16]. The most useful echocardiographic views to delineate the margins of the window include the suprasternal long axis, the subcostal coronal plane through the pulmonary trunk, and the high parasternal short plane cephalad to the aortic valve.

Magnetic resonance imaging is an emerging technique that is capable of clarifying anatomy with great detail [17].

Cardiac catheterization (Fig. 95.2) is indicated to determine operability in children diagnosed beyond infancy with features suggestive of PAH and also in cases of associated coronary abnormality to delineate the coronary anatomy. The differential diagnosis of APW includes PDA, truncus arteriosus, VSD with aortic insufficiency, and ruptured sinus of Valsalva aneurysm.

Natural History

Patients with large APW generally do not survive beyond childhood. Of untreated patients, 40% die within the first year of life [18]. Untreated patients generally develop pulmonary vascular obstructive disease.

Only 32 patients over 20 years of age have been described [2, 4, 5, 11, 15, 19–27]. The oldest was 58 years of age [15], had pulmonary vascular disease, and died from an unassociated aortic valve lesion. Patients over 10 years of age seldom have associated complex heart disease, although they may have simpler lesions such as a bicuspid aortic valve, coarctation of the aorta or a VSD. They usually have pulmonary vascular disease unless the defect is very small.

Infective endocarditis is rare [23, 27].

In part the natural history depends on the severity of associated lesions. Furthermore, because an APW is rare, it is particularly difficult to estimate the natural history. Because of the poor prognosis associated with this condition, it is recommended that all patients with APW undergo repair.

Management

Medical and Interventional Therapy

The medical therapy for an APW is the same as for a large PDA. There have been reports on successful transcatheter closure of APW [25, 28, 29] but the success using this approach requires secure positioning of the device to occlude the orifice of the APW without impinging on the ostium of the left coronary artery. Following device closure, patients need to be followed for the development of aortic regurgitation at the time of the *procedure as well as long-term.*

Surgical

Indications

Operative treatment is indicated as soon as the diagnosis is established, regardless of the patient's age. Unless there is a right-to-left shunt despite oxygen administration, no patients with APW should be denied the operation [11]. Elective repair is advised before age 3 months.

Technique of Operation

There are several surgical techniques described with success (Table 95.1) but the most widely accepted optimal approach is the one described by Johansson and colleagues (sandwich type repair) [36].

Table 95.1 Evolution of surgery for aortopulmonary window

Year	Surgeon	Method
1948	Gross [5]	Ligation
1953	Scott and Sabiston [30]	Division without cardiopulmonary bypass
1957	Cooley et al. [31]	Division with cardiopulmonary bypass
1966	Putnam and Gross [32]	Transpulmonary patch closure
1968	Negre et al. [33]	Anterior sandwich patch closure
1968	Wright et al. [34]	Transaortic suture closure
1969	Deverall et al. [35]	Transaortic patch closure
1978	Johansson et al. [36] Aberg [37]	Single patch sandwich type repair
1987	Shatapathy et al. [38]	Pulmonary artery flap closure
1992	Matsuki et al. [39]	Anterior pulmonary artery flap closure

APW is approached through standard midline sternotomy. Diagnosis confirmed when separate semilunar valve "anuli" can usually be verified by finding a dimple between the two great arteries where they arise from the heart (Fig. 95.3a) which differentiates it from truncus arteriosus.

Cardiopulmonary bypass is established using bicaval venous and distal aortic cannulation. Bilateral pulmonary arteries are snared and kept. Most cases are dealt under moderate hypothermia unless the infant weighs less than 2.5 kg wherein deep hypothermic circulatory arrest may be used. Aorta is cross clamped and antegrade cardioplegia is delivered after snaring the bilateral branch pulmonary arteries. Left atrium can be vented through the PFO after right atriotomy. An incision is made in the anterior wall of the communication between the aorta and the pulmonary trunk (Fig. 95.3b). A PTFE patch is then sutured to the posterior wall of the defect. The suture line is subsequently carried anteriorly to incorporate the patch in the closure of the arteriotomy.

In the transaortic approach [35] for the repair of APW, a longitudinal aortotomy is made in the ascending aorta. For simple proximal (type I) defects, closure is readily accomplished using a polyester, PTFE or pericardial patch. Care must be taken to identify the left coronary orifice. For distal (type II) defects, a more extensive patch must be fashioned. When there is considerable unroofing of the right pulmonary artery, the creation of an intra-aortic baffle and closing the aortotomy with an elliptical patch may suffice. Total (type III) and intermediate type defects are repaired using similar techniques.

In pulmonary flap technique [38], an anterior flap of pulmonary artery is incised in continuity with the aorta along the anterior border of the window. The anterior flap is then sewn to the posterior margin of the APW, thereby closing the defect in the aorta. The resultant defect in the pulmonary artery is then closed with a patch (autologous or heterologous).

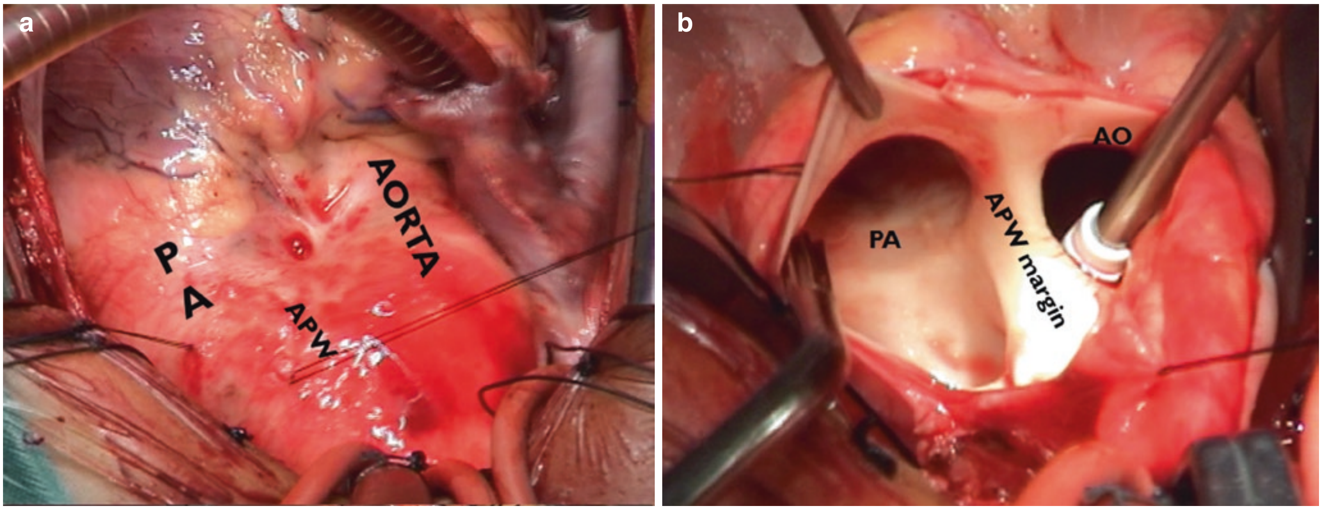

Fig. 95.3 Operative photograph showing (**a**) large sized aortopulmonary window (APW) externally (**b**) after opening the APW

Kitagawa and associates [40] reported an alternative technique to repair a distal APW with extensive unroofing of the right pulmonary artery. In this approach, the ascending aorta is transected at the distal extent of the window, and the right pulmonary artery is excised along with a strip of posterior aorta in continuity with the window and pulmonary trunk. The defect in the pulmonary artery is then repaired either primarily or using a patch, and the aorta is reconnected primarily. This technique has the advantage of avoiding any potential problems resulting from an intra-aortic baffle.

Associated cardiac anomalies are repaired in a same setting as far as possible.

Postoperative Management

Intraoperative transesophageal echocardiography is useful for confirming complete closure of the defect and ensuring that the pulmonary arteries have not been narrowed. Management of PAH post operatively in patients presenting later in life is the most crucial part. PA catheter is best suited in managing such patients. Inhaled nitric oxide, phosphodiesterase inhibitors, endothelin receptor antagonist, fentanyl and muscle relaxants, and mild hyperventilation with 100% oxygen can be used in preventing pulmonary hypertensive crisis.

Results

The results of surgical treatment of APW demonstrate low risk, even if the APW is associated with major cardiac anomalies. Surgical options are tailored to the anatomy and the size of the defect. Whenever possible, continuity ligation, division and suture should be done with cardiopulmonary bypass on standby. This approach reduces the potential complications of cardiopulmonary bypass, avoids blood requirements, and reduces the hospital stay, thus leading to lower morbidity. Long-term outcome after operative correction is excellent regardless of age or PVR [11]. For patients with complex associated anomalies, the prognosis is determined largely by the presence of associated anomalies.

Conclusion

APW is a rare but well identified and surgically correctable anomaly. Operative repair should be offered as soon as the diagnosis is established, regardless of the patient's age. Irreversible PAH with a right to left shunt despite oxygen administration is the only contraindication for surgery. Various surgical techniques can be applied depending on the size of the communication. Associated arch anomalies may require technically challenging approaches and surgical strategies. Early and long-term outcomes after surgical correction are excellent regardless of age or PVR.

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Coarctation of the Aorta

96

Shafi Mussa and David R. Anderson

Introduction

Coarctation of the aorta is defined as a discrete narrowing of the aortic lumen. The vast majority of cases are found in the region of the aortic isthmus (the part of the aorta distal to the origin of the left subclavian artery and proximal or adjacent to the insertion of the ductus arteriosus), although there are instances when the aortic narrowing has been found more distally in the descending thoracic or abdominal aorta.

It is distinct from interrupted aortic arch in which there is complete luminal discontinuity of the aorta, and from diffuse tubular hypoplasia of the aortic arch in which the whole aortic arch is narrowed. There are however many children with this latter condition in whom a narrow transverse arch tapers down to a coarctation, and in some cases interruption of the aortic arch with fibrous aortic continuity.

Coarctation is a common lesion, accounting for approximately 6% of all congenital heart disease. It is twice as common in males compared to females. It is more prevalent in genetic syndromes such as Turner's syndrome.

Morphology

A ridge of tissue extends into the aortic lumen from the posterior and lateral wall of the aorta causing an obstruction to blood flow. Common associations include bicuspid aortic valve and ventricular septal defect. Coarctation is also seen in the context of more complex congenital heart lesions such as hypoplastic left heart syndrome and Shone's syndrome (supramitral membrane, parachute mitral valve, sub-valvar and valvar aortic stenosis, and coarctation). It virtually never accompanies right heart lesions such as tetralogy of Fallot, pulmonary atresia and tricuspid atresia [1].

Pathophysiology and Clinical Presentation

In utero and during the first hours and days of life the ductus arteriosus remains patent and allows blood to flow beyond the coarctation segment (Fig. 96.1). As the levels of maternal prostaglandins drop, the smooth muscle in the wall of the ductus arteriosus contracts. Closure of the ductus arteriosus usually occurs at day 2 to day 4 of life and exposes the aortic narrowing, leading to:

- Obstruction to systemic blood flow
- Increased left ventricular afterload
- Hypoperfusion distal to the coarctation segment.

The degree of obstruction to flow, increased ventricular afterload, and distal hypoperfusion is dependent on the severity of the narrowing, which in turn governs the clinical presentation [1].

Fetal Presentation

Where available, pre-natal imaging increasingly detects in utero abnormalities that raise a suspicion of coarctation. Fetal echocardiography from 18 weeks of gestation can demonstrate suggestive findings such as ventricular disproportion (the left ventricle not forming the cardiac apex or appearing obviously smaller than the right ventricle), presence of left superior vena cava, and retrograde flow in the aortic isthmus. Fetal magnetic resonance imaging is currently being developed as the latest diagnostic tool and is particularly useful for structural aortic malformations.

Neonatal Presentation

A critical aortic narrowing exposed by closure of the ductus arteriosus can lead to neonatal collapse due to sudden obstruction to systemic blood flow and splanchnic and lower

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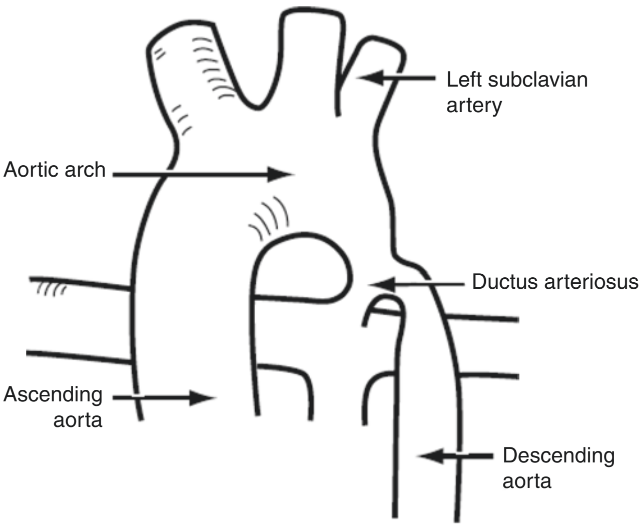

Fig. 96.1 Diagram of the fetal circulation in coarctation. The aorta is discretely narrowed adjacent to the insertion of the ductus arteriosus. While the ductus arteriosus remains patent and allows blood to flow unimpeded into the descending thoracic aorta. Closure of the ductus arteriosus leads to a narrower passage and restriction to blood flow

limb hypoperfusion. The patient will be pale, shocked, tachypnoeic, and anuric. Examination may reveal weak or absent femoral pulses, and murmurs consistent with coarctation and associated defects. There may be features of necrotizing enterocolitis (abdominal distension, bloody stools).

Infant Presentation

Less commonly, a severe coarctation that may have gone unnoticed in the neonatal period will cause chronic afterload for the left ventricle. The immature myocardium does not tolerate this well and may hypertrophy initially, but eventually the left ventricle will begin to dilate and fail. Infants may present in significant heart failure secondary to a dilated, poorly functioning left ventricle at about 6 weeks of age and onwards. The main features are poor feeding, failure to thrive, tachycardia, poor peripheral perfusion, and weak or absent femoral pulses.

Childhood/Adolescent/Adult Presentation

Coarctation can be asymptomatic and may indeed go unnoticed for many years. Blood bypasses the narrowed aortic segment by development of collateral vessels (enlargement of existing vasculature e.g. the internal thoracic and intercostal arteries), maintaining distal perfusion. The clinical presentation is therefore often of insidious upper limb hypertension, although leg claudication has also been described. Other signs are radio-femoral delay, a systolic murmur that typically radiates to the back, and rib notching on the chest radiograph (deformation of the inferior surface of the ribs due to collateral vessels). Rarely, coarctation may present in association with a related cardiac condition such as bicuspid aortic valve or as a consequence of ascending aortic dissection.

Uncorrected coarctation is often fatal in neonates and infants, and in patients who present later in life leads to a reduced life expectancy of 30–40 years, with causes of death including aortic rupture, intracranial haemorrhage, cardiac failure, accelerated coronary artery disease, and endocarditis. There remains a lifetime risk of hypertension, even if coarctation is corrected early in life.

Diagnosis

Echocardiography

This is the mainstay of diagnostic imaging in coarctation, particularly in neonatal and infant presentations. Fetal echocardiography may have raised a suspicion of the diagnosis and early post-natal echocardiography is then essential to confirm the diagnosis.

Reduced pulsatility of the descending thoracic and abdominal aorta on a long axis view is a reliable sign of coarctation. A high long axis parasternal view will show the coarctation segment, often as a classical “3” appearance (Fig. 96.2), and the ductus arteriosus (if patent). A posterior aortic shelf may be seen. Turbulence and increased flow velocity in the isthmus, in addition to diastolic extension of flow (often termed ‘diastolic tailing’) in the descending thoracic aorta giving a saw-tooth appearance on continuous wave Doppler are very reliable diagnostic features (Fig. 96.3). A supra-sternal view of the aortic arch can also reveal the coarctation segment and provide a view of the proximal and distal parts of the aortic arch, demonstrating any diffuse narrowing or tapering of the arch as it continues towards the isthmus, as well as giving an indication of the number and branching pattern of the supra-aortic vessels.

Once the diagnosis is confirmed it is mandatory to complete a full assessment of the heart to exclude associated lesions, and to confirm the adequacy of left heart structures (mitral valve, left ventricular cavity, the sub-aortic region, aortic valve, and ascending aorta). The assessment of ductal patency is key to further management, and serial scans to assess the impact of medical intervention are often necessary.

Finally, direct measurement of arch dimensions can indicate associated transverse arch hypoplasia requiring surgical relief or whether isolated repair of coarctation will suffice. In practical terms, the transverse arch diameter should measure the weight of the baby plus 1 mm i.e. a baby weighing 3 kg would be expected to have a transverse aortic arch measuring 4 mm or more. An additional indication of transverse arch

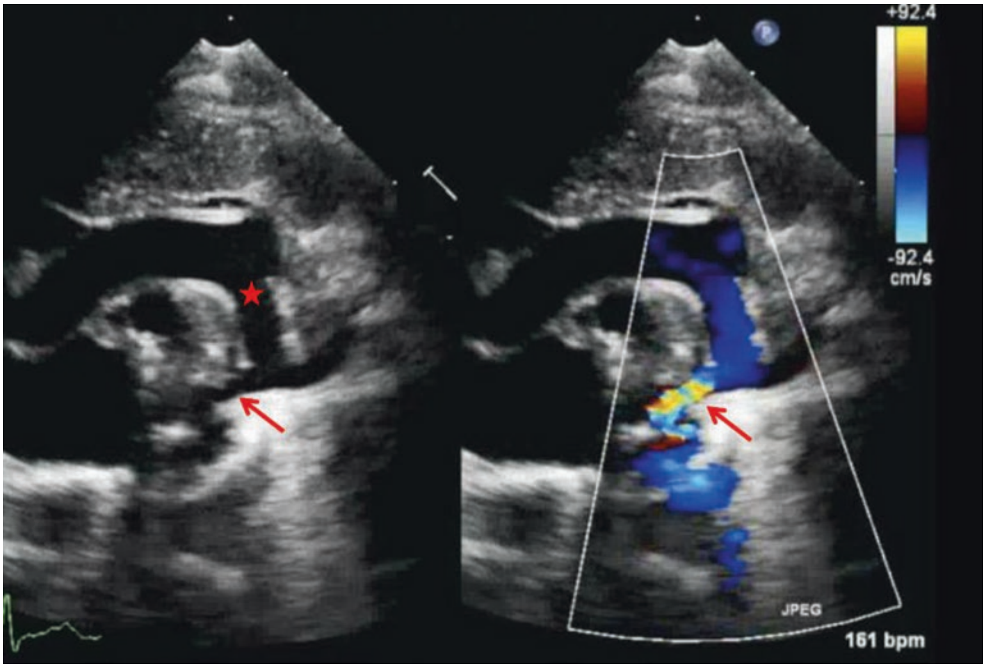

Fig. 96.2 *Left panel* – High long axis parasternal echocardiogram demonstrating the transverse aortic arch (red star) and coarctation of the aorta (red arrow). *Right panel* – High long axis parasternal echocardiogram with colour Doppler demonstrating turbulence at the narrow part of the aorta (red arrow)

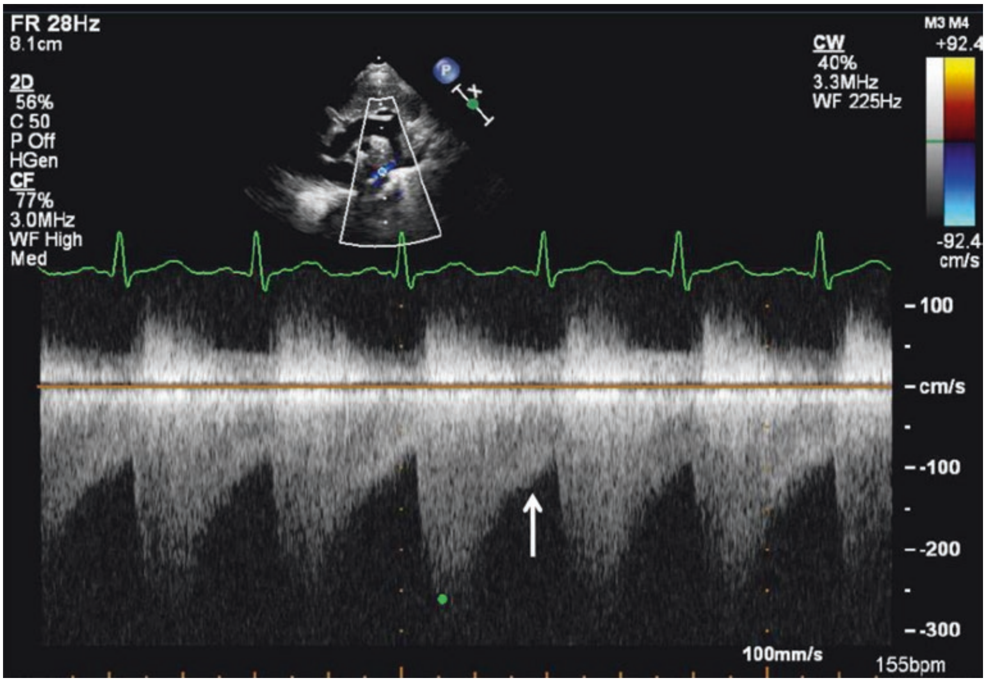

Fig. 96.3 Continuous wave Doppler echocardiogram demonstrating prolonged antegrade flow of blood through the coarctation segment in diastole, termed “diastolic tailing” (white arrow)

hypoplasia is if the proximal transverse arch (between brachiocephalic trunk and left common carotid) is less than 60% of the diameter of the ascending aorta, if the mid transverse arch (between left common carotid and left subclavian artery) is less than 50% of the ascending aortic diameter, and if the distal arch (between left subclavian artery and aortic isthmus) is less than 40% of the ascending aortic diameter. Measurements of less than this warrant additional imaging to define precisely the anatomy [2].

Computed Tomography Scanning

Increased spatial and temporal resolution, faster acquisition times, reduced requirement for ionizing radiation and intravenous contrast, and ability to re-format datasets into accessible 2D and 3D reconstructions mean that cardiac computed tomography (CT) is a safe, valuable and pragmatic tool to evaluate aortic disease in all age groups. It is now the second line investigation in the assessment of coarctation in neonates and infants, and is used with increasing frequency when there is a need to delineate more complex anatomy following echocardiography. 3D reconstructions of the aorta from the aortic root to the descending thoracic aorta provide detailed anatomical information, precise measurements, and relationships to other intrathoracic structures (Fig. 96.4). This enables advanced planning of surgical strategy and reduced reliance on intra-operative decision-making.

Magnetic Resonance Imaging

Magnetic resonance (MR) does not involve ionizing radiation and provides functional data, but poorer spatial resolution than CT and more need for patient cooperation (long breath holds to acquire data) mean that it is a less suitable imaging modality for coarctation and aortic arch evaluation in younger children unless general anaesthesia is used. However, the combination of detailed anatomical and functional data make it an excellent modality for the evaluation of coarctation in older children and young adults. MR is also useful in follow-up as serial scans provide objective comparative data, and can be undertaken without increasing the radiation burden for any one individual. Contrast enhanced magnetic resonance angiography is the preferred technique for imaging the aorta and collateral vessels (Fig. 96.5), as it is reliable and robust and can be completed within 20 minutes. Time-resolved, 3D MR scanning, so-called 4D MR, allows visualisation and quantification of flow and can be used to analyse abnormal flow patterns and turbulence but has yet to enter routine clinical practice.

Catheterisation and Angiography

Originally, this was the gold standard for aortic imaging in older children and adults but has now been superseded by non-invasive modalities such as CT and MR imaging. Where these are not available, it remains a valuable diagnostic tool. It also has the additional advantages of enabling transcatheter therapeutic options and providing additional diagnostic information (e.g. coronary artery angiography) in adults prior to intervention.

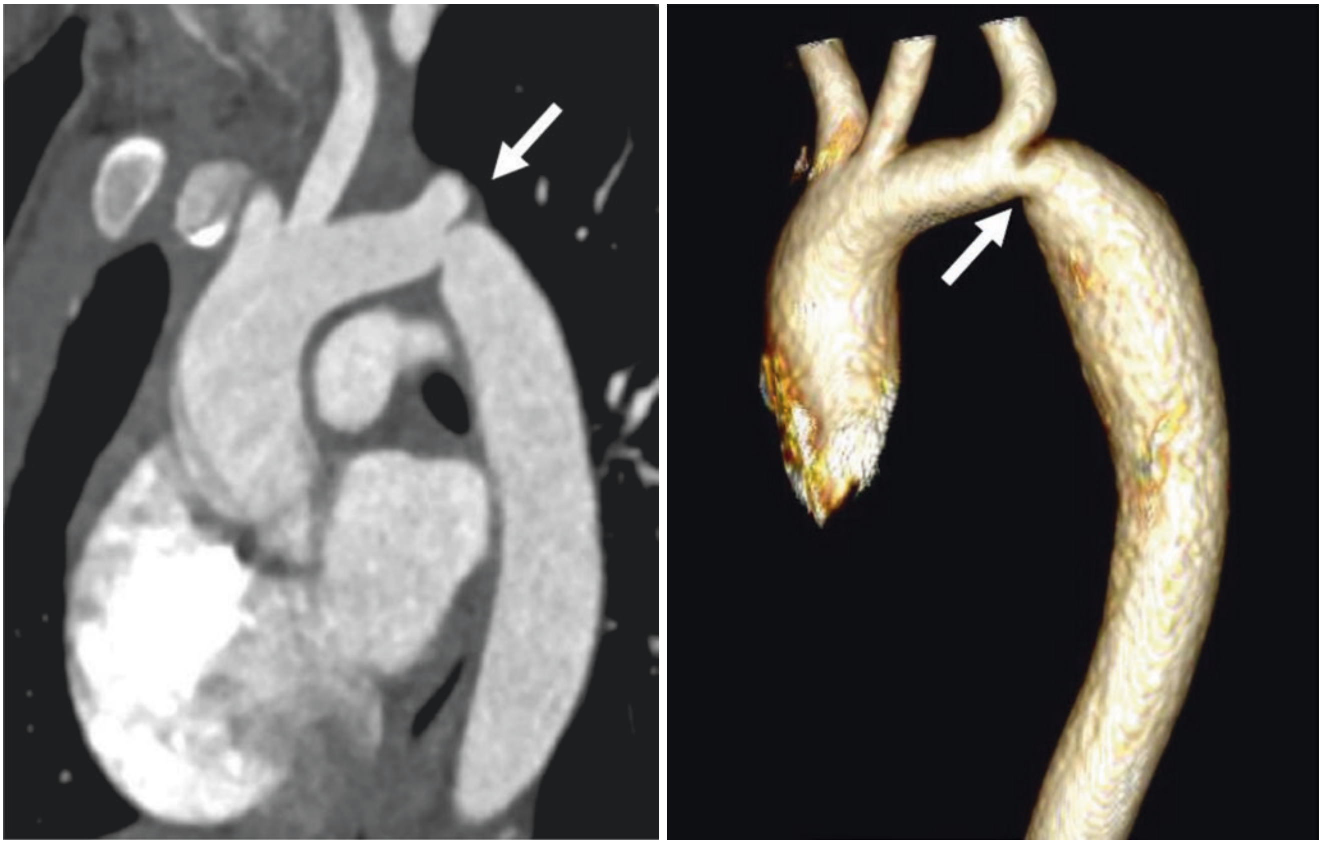

Fig. 96.4 *Left panel* – Computed tomography scan of the aorta (sagittal view with intravenous contrast) demonstrating coarctation (which arrow). *Right panel* – 3D reconstruction of the aorta in the same patient showing detailed morphology of the aortic arch, coarctation segment (white arrow) and supra-aortic vessels

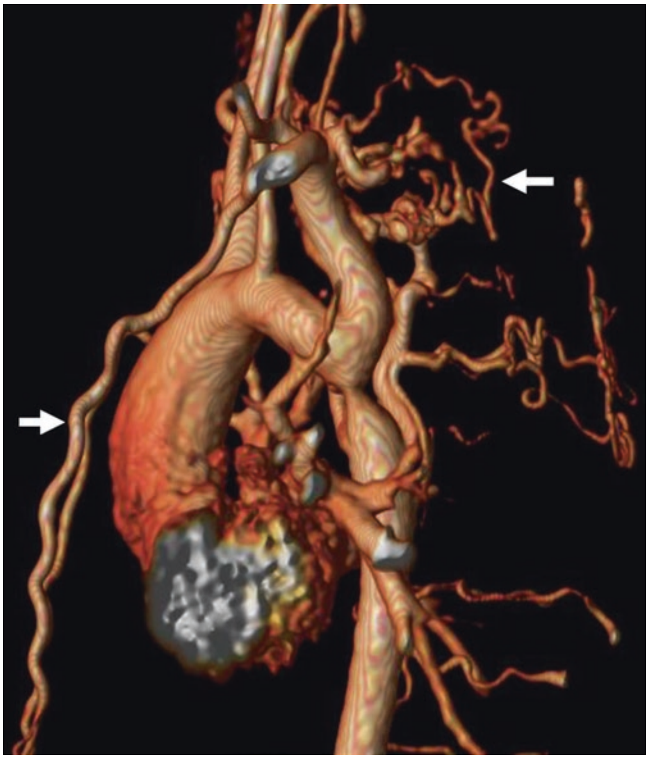

Fig. 96.5 Magnetic resonance angiogram. 3D reconstruction of the aorta showing detailed morphology of the aortic arch, coarctation segment and collateral vessels (white arrows)

Initial Management

Fetal presentation. For pre-natal diagnosis of coarctation, delivery should be planned to take place in a cardiac centre, with early post-natal echocardiographic assessment, intravenous prostaglandin infusion to maintain patency of the ductus arteriosus started at the earliest opportunity, and then serial clinical and echocardiographic assessment to inform definitive treatment. There may be some features of coarctation on pre-natal imaging but the overall suspicion may be low. In this case, prostaglandin infusion may be withheld and serial clinical (4 limb blood pressure) and echocardiographic assessment is undertaken to see if coarctation develops.

Neonatal presentation. In the collapsed neonate the most important initial step in management is to attempt to re-open the ductus arteriosus with an intravenous prostaglandin infusion. Further resuscitative measures such as ventilation and inotropic support may be required. As the ductus re-opens lower body perfusion is restored and the clinical condition of the baby should improve and stabilise. Definitive treatment should be undertaken at the earliest opportunity.

Infant presentation. For the infant presenting in cardiac failure with coarctation and poor left ventricular function, ventilation and resuscitation with inotropes may be necessary to improve the general condition of the child before embarking on definitive treatment. If these measures are not sufficient, or the required doses of inotropes are harmful, either balloon angioplasty or mechanical circulatory support in the form of extracorporeal membrane oxygenation (ECMO) can be used to temporise and improve the general condition of the child before undertaking definitive treatment.

Child/Adolescent/Adult presentation. Older patients present less acutely, and often require management of hypertension with beta-adrenergic antagonists in the first instance. Appropriate imaging and definitive treatment can be arranged in due course.

Definitive Treatment

In the vast majority of cases, neonatal and infant coarctation is treated with surgery [3, 4]. Rarely, some neonates do not respond to a prostaglandin infusion or would be better served by waiting before surgical intervention and may benefit from a temporising balloon angioplasty. The baby can then be stabilised before undertaking a surgical repair. Conversely, children, adolescents and adults with coarctation are treated predominantly by transcatheter approaches [5], and only undergo surgery if transcatheter techniques are not suitable.

Surgery for Coarctation in Neonates and Infants

There are two main surgical approaches to coarctation:

- Left thoracotomy without the use of cardiopulmonary bypass
- Median sternotomy with the use of cardiopulmonary bypass.

Left Thoracotomy Without Cardiopulmonary Bypass

This approach is usually employed for discrete coarctation and coarctation with distal arch hypoplasia, with no concomitant cardiac lesions that need to be addressed concurrently. The approach enables a coarctation to be repaired by four options:

- Resection and end-to-end anastomosis
- Subclavian flap aortoplasty
- Patch aortoplasty
- Resection and extended end-to-end anastomosis.

Resection and end-to-end anastomosis involves excision of the coarctation segment including all ductal tissue from the aorta and then fashioning a circumferential anastomosis between the proximal and distal descending thoracic aorta (Fig. 96.6a). It is the simplest surgical option, but is only suitable if the coarctation can be excised without affecting the origin of the left subclavian artery and has a relatively high rate of re-coarctation (c.10%).

Subclavian flap aortoplasty requires the subclavian artery to be mobilised, ligated distally (but proximal to the origin of the vertebral artery), divided, and then incised along the lateral aspect to produce a flap or tongue of tissue. The incision is then extended caudally along the lateral aspect of the aorta, laying it open through the coarctation segment, so that the flap of subclavian artery can be folded down and used to augment the aorta (Fig. 96.6b). This option is useful for a longer narrowing but sacrifices the antegrade flow in the subclavian artery and relies on retrograde flow from the vertebral artery to perfuse the left arm. The ductal tissue should be enucleated if possible to avoid the occurrence of re-coarctation as it involutes.

Patch aortoplasty requires the lateral aspect of the aorta to be incised through the coarctation segment, and then augmented using an elliptical patch of non-autologous material (Fig. 96.6c). Similarly to a subclavian flap aortoplasty the ductal tissue should be enucleated to avoid future re-coarctation. There is a risk of false aneurysm formation at the suture lines, and for that reason this technique is rarely used in contemporary practice.

Resection and extended end-to-end anastomosis involves excision of the coarctation segment and all ductal tissue from the aorta, but the anastomosis is elongated by virtue of extending the incision in the proximal segment along the concavity of the aortic arch and also creating a counter-incision in the posterior wall of the descending thoracic aorta. The resulting anastomosis is therefore more elliptical and wider (Fig. 96.6d).

In contemporary practice, the preferred option is resection and extended end-to-end anastomosis as this has the lowest rate of re-coarctation.

Surgical Technique

Following general anaesthesia, right radial and femoral arterial lines are inserted in order to determine the invasive arterial pressure both proximal and distal to the aortic arch, and also any pressure gradient across the anastomosis once the repair is completed. Some surgeons advocate non-invasive cerebral monitoring and urinary catheter insertion.

The patient is placed in a right lateral decubitus position and the chest is entered via a left posterolateral thoracotomy through the fourth intercostal space. The left lung is retracted anteriorly, the pleural reflection overlying the descending thoracic aorta is divided, and the dissection is extended to expose the coarctation segment, the proximal descending thoracic aorta, the proximal left subclavian artery, the ductus arteriosus and the aortic arch proximally to the origin of the brachiocephalic trunk. Care must be taken to avoid injury to the vagus nerve and its left recurrent laryngeal branch, the thoracic duct and the oesophagus. The dissection is continued on the posteromedial aspect of these structures such that they are fully mobilised from the investing fascia. The intercostal vessels can either be controlled with fine silk ligatures or cauterised and divided. The ductus arteriosus is then ligated as close to the pulmonary artery as possible. Appropriate clamps are positioned on the aortic arch incorporating the proximal left subclavian and left common carotid arteries (usually a curved clamp) and descending thoracic aorta (usually straight and angled). Once the clamps are applied, the elasticity of the aorta can be tested to confirm the ends will come together without excessive tension. The coarctation segment then is excised and all ductal tissue is removed from the aorta. The incision in the proximal aortic segment is extended along the concavity of the arch and an appropriate counter-incision is made in the posterior wall of the distal aortic segment. A continuous fine monofilament (e.g. 6-0 or 7-0 polypropylene) suture is then used to form a wide elliptical anastomosis between the two ends. Following haemostasis an intercostal drain is placed and the chest is closed.

Specific Complications, Advantages, Disadvantages and Alternative Treatments

The structures at risk during this approach are the recurrent laryngeal nerve and the thoracic duct, and injury will result in ipsilateral vocal cord palsy and chylothorax respectively. The incidence of paraplegia as a result of spinal cord ischaemia is extremely low after neonatal or infant repairs due to relatively short clamp times (<20 min) and deliberate permissive mild hypothermia during surgery, which has a protective effect on the cord. Aortic clamping for over 30 min increases the risk of paraplegia (Table 96.1).

The advantage of this approach is that it is relatively straightforward and therefore low risk surgery with none of the risks of cardiopulmonary bypass. The main disadvantage is that it is only suitable for isolated coarctation repair. The interventional alternative of balloon dilatation has a relatively high rate of re-coarctation due to elastic recoil of the aorta (up to 80% recurrence rates within a few months) and is therefore reserved as a temporising measure for high-risk patients with critical coarctation in whom waiting for improvement in ventricular and/or renal function would be of benefit prior to surgery. However, in those patients who are found to have re-coarctation following surgical repair, balloon dilatation is the treatment of choice.

Fig. 96.6 Diagram of surgical techniques for repair of coarctation. (**a**) Resection with end-to end anastomosis. (**b**) Subclavian flap aortoplasty. (**c**) Patch aortoplasty. (**d**) Resection and extended end-to-end anastomosis

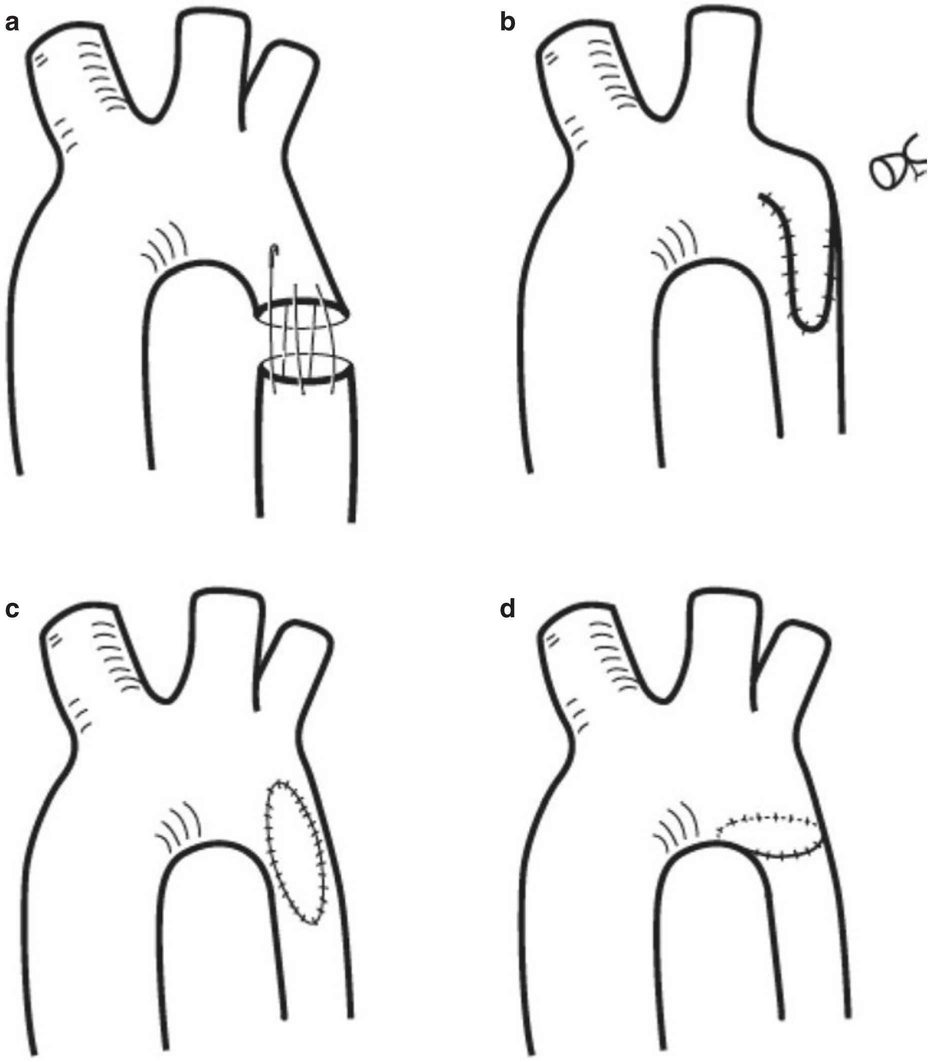

Table 96.1 Comparison of post-operative complications associated with the two approaches for coarctation repair in neonates and infants

	Thoracotomy without cardiopulmonary bypass	Median sternotomy with cardiopulmonary bypass
Recurrent laryngeal nerve injury	√	√
Vagus nerve injury	√	
Phrenic nerve injury		√
Thoracic duct injury	√	√
Bleeding		√
Infection	√	√
Post-operative pain	√	
CPB related complications		√
Left main bronchus compression		√
Spinal cord injury	√	√
Brain injury		√

CPB cardiopulmonary bypass

Median Sternotomy with Cardiopulmonary Bypass

This approach is usually employed when a satisfactory repair cannot be achieved via a left thoracotomy or if there is an associated lesion that needs cardiopulmonary bypass for repair. The two most common situations are:

- Hypoplasia of the proximal or transverse aortic arch with or without discrete coarctation.
- Coarctation associated with a ventricular septal defect.

Surgical Technique

Following general anaesthesia, right radial and femoral arterial lines are inserted in order to determine the invasive arterial pressure both proximal and distal to the aortic arch, and also any pressure gradient across the anastomosis once the repair is completed. Urinary catheter insertion is mandatory for all cases requiring cardiopulmonary bypass. Non-invasive cerebral monitoring is desirable.

The heart and great vessels are exposed via median sternotomy. Cerebral blood flow will be compromised when the entire aortic arch is isolated, and a cerebral protection strategy must be adopted. This is achieved either by deep hypothermia and circulatory arrest, or moderate hypothermia and selective antegrade cerebral perfusion, and the cannulation strategy differs depending on the favoured approach.

Deep hypothermia can be achieved via cannulation of the ascending aorta, any appropriate venous drainage, and cooling to the desired temperature once cardiopulmonary bypass has been started (nasophayngeal temperature is measured as it best reflects brain temperature). Topical ice packs around the head are also employed. The arterial duct is ligated as it emerges from the pulmonary arteries. Once at desired temperature, following cardioplegic arrest and total circulatory arrest, the ascending aorta is clamped, the aortic cannula can be removed if necessary, the supra-aortic vessels are snared just beyond their origins, and the descending aorta is clamped to isolate the aortic arch. All ductal tissue is excised or enucleated and the arch can then be laid open by incising along its concavity until just beyond the proximal extent of the narrowing. The arch is augmented, either with a patch of suitable material (e.g. donor pulmonary homograft) or by an extended end-to side technique depending on the proximal extent of the narrowing, availability of homograft material and other practical concerns. Once the reconstruction is completed, air is evacuated from the aorta, the clamps and snares are removed and the circulation is re-commenced, rewarming to normothermia.

Selective antegrade cerebral perfusion can be achieved by mobilizing and isolating the brachiocephalic trunk in a side-biting clamp, performing a longitudinal arteriotomy, and anastomosing a 3.5 or 4 mm diameter GoreTex conduit to the opened artery in an end-to side fashion. An appropriate sized arterial cannula is then inserted into the GoreTex tube and secured, before de-airing the cannula and connecting to the bypass circuit. Following venous cannulation bypass is commenced, the duct is tied, and the patient is cooled. Ice packs are placed around the head. Once at desired temperature, the ascending aorta is clamped and cardioplegic arrest is induced, the supra-aortic vessels are snared just beyond their origins, and pump flow is reduced by approximately two thirds. In this way both cerebral perfusion and a bloodless field are maintained in order to reconstruct the aortic arch. Right radial arterial pressure gives an indication of cerebral arterial pressure, as the radial artery is direct continuity with the brachiocephalic trunk, and should be monitored closely together with non-invasive cerebral monitoring during the period of selective cerebral perfusion. Once the arch repair is completed and the aorta is de-aired, the supra-aortic snares and aortic cross-clamp are released, whole body perfusion is re-commenced, bypass flow is increased to full flow, and the patient can be warmed to normothermia.

Additional procedures such as VSD closure can be performed during either the cooling or rewarming phase of the bypass run depending on surgical preference. Bypass is then discontinued, the heart decannulated, and the chest can be closed following haemostasis and placement of drains and pacing wires as appropriate.

Specific Complications, Advantages, Disadvantages and Alternative Treatments

The recurrent laryngeal nerve and thoracic duct are also at risk during this approach, and ipsilateral vocal cord palsy and chylothorax are recognised complications. Although it is possible to mobilise the proximal descending aorta sufficiently to create an anastomosis with the proximal arch thereby avoiding donor patch material there is a distinct risk of compression on the left main bronchus as it passes under the reconstructed arch. This direct anastomosis technique should only be used if there is ample space under the arch as it is extremely difficult to relieve the bronchial compression at a later stage. The incidence of paraplegia is similarly low to non-bypass approaches (Table 96.1).

The main advantage of this approach is versatility, as it enables the surgeon to repair all types of aortic arch lesions and also any associated intra-cardiac lesions. The main disadvantage is the requirement for cardiopulmonary bypass, which precludes patients of very low birth weight, those with significant haemorrhagic risk, and those with significant septic concerns. Balloon angioplasty of the aortic arch is a technically challenging potential alternative transcatheter approach. However, with poor outcomes from previous attempts, it is only used in extreme situations when resuscitation is required to prior to definitive surgical repair.

Treatment of Coarctation in Older Children and Adults

Surgical repairs in older children and adults are more technically challenging, primarily because the reduced tissue elasticity often precludes resection and end-to-end anastomosis, and alternative techniques such as patch aortoplasty or placement of interposition grafts need to be considered. Additional but surmountable challenges are the collateral vessels in the thoracic wall leading to possible significant haemorrhage during the incision, and access to the distal aortic arch and descending thoracic aorta via both median sternotomy and left thoracotomy approaches in larger patients with correspondingly larger thoracic dimensions. Due consideration needs to be given to spinal cord protection and maintenance of splanchnic and lower limb perfusion, although this may be less concerning in severe coarctation with well-developed collateral vessels.

Alongside this there have been considerable advances in endovascular techniques and stent technology. Outcomes from interventional approaches to coarctation in older children and adults are comparable to surgery in terms of procedural success and re-intervention rates, but with a lower rate of procedural complications. Balloon aortoplasty and stenting are now the first line of treatment for coarctation in this group. Stents can be implanted in children and serially dilated as the patient grows. Children with aortas that approach half of adult diameter can be treated with stent implantation. In severe coarctation a stent can be implanted and then dilated up to normal aortic diameter in a staged fashion [5].

Outcomes in Contemporary Practice

Recent outcome data from the United Kingdom National Congenital Heart Disease Audit (2014–2017) shows that surgical repairs for isolated coarctation/hypoplastic arch were undertaken in 721 paediatric patients and 19 adult patients. Thirty-day survival in the paediatric group was 99.4% (4 deaths), and 100% in the adult group [3].

Over the same time period, balloon dilatation of native coarctation was undertaken in 97 patients (90 paediatric patients) with a 30-day survival of 95.9% (4 deaths, all in the paediatric group). Interventional procedures are therefore less commonly performed as a treatment for native coarctation, and the lower survival reflects the higher risk of patients that need treatment but are not suitable for surgery.

Balloon dilatation of re-coarctation was undertaken in 251 patients (232 paediatric) with a 30-day survival of 98.9% (4 deaths, all in the paediatric group), the implication being that re-coarctation can be successfully treated with relatively low risk.

Long-Term Follow-Up

Ongoing surveillance following coarctation repair is necessary with a focus on management of persistent hypertension, and the development of re-coarctation and false aneurysms related to suture lines and endovascular stents.

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Pulmonary Valve Stenosis

97

Fazal W. Khan and M. Sertaç Çiçek

High Yield Facts

- Obstruction to pulmonary blood flow may occur at different levels with valvar pulmonary stenosis being the most common variant.
- The presentation and clinical manifestations depend on the age, severity of the obstruction and associated cardiac defects.
- Pulmonary balloon valvotomy is well established as the gold standard initial intervention, with excellent short- and long-term outcomes.
- Neonates with critical PS require urgent intervention, including prompt administration of prostaglandin E1 to maintain patency of the ductus arteriosus followed by definitive intervention once the neonate is medically stabilized.
- For patients with severe PS (gradient >60 mmHg) catheter-based or surgical intervention is recommended.
- Surgery is reserved for failed catheter interventions, multi-level obstructions, complex cases or need for additional source of pulmonary blood flow.

Introduction

Pulmonary valve stenosis is a common entity, compromising 8–10% of all cardiac malformations. It usually is an isolated lesion, however might be associated with many types of congenital heart lesions such as tetralogy of Fallot, double outlet right ventricle, d-transposition of great arteries, single ventricles and others. Acquired causes of pulmonary stenosis are significantly less common and include carcinoid heart disease, rheumatic heart disease, and infective endocarditis. The vegetations and plaques that develop because of these conditions are responsible for the stenosis. This chapter will mainly address isolated pulmonary stenosis.

Anatomy and Spectrum of Lesions

Pulmonary stenosis (PS) may occur above, at or below the pulmonary valve with obstruction at the valvar level has been reported to be the most common lesion.

Valvar PS: Stenosis at the valvar level is typically characterized by fused or absent commissures with thickened leaflets of the pulmonary valve. In most patients, the valve is a dome-shaped structure with a small orifice [1, 2]. It is the most common type accounting for 80–90% of cases of right ventricular outflow tract (RVOT) obstruction [3]. The stenotic valve is usually thickened with fusion of leaflets at the commissures extending towards the center. It is further divided into three clinically significant morphologies: domed with no commissures, dysplastic, and bicuspid/multicuspid. Dysplastic pulmonary valves are less common, these valves are often irregular with prominent leaflet thickening leading to a small (hypoplastic) valve annulus and reduced mobility. This anatomic variant is associated with Noonan syndrome or other syndromes [4]. Pulmonary valvar stenosis is almost always accompanied by RV hypertrophy when severe, which might resemble a clinical picture of pulmonary atresia with intact ventricular septum.

Subvalvar PS: Isolated subvalvar PS is uncommon and caused by primary fibromuscular narrowing below the pulmonary valve. It is either associated with other congenital cardiac conditions including double-chambered RV and tetralogy of Fallot (TOF) [5] or an associated ventricular septal defect which might have closed spontaneously.

Supravalvar PS: Supravalvar PS is defined as a discrete narrowing of the main pulmonary artery (PA), located just

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above the pulmonary valve. Isolated congenital supravalvar PS is very rare and most commonly seen in iatrogenic post-surgical repair including TOF, D-transposition of the great arteries, and pulmonary artery band placement and removal. It may be associated with genetic syndromes like Williams syndrome.

Peripheral PS: Peripheral PS refers to discrete areas of narrowing in the pulmonary arteries that can be unilateral, bilateral, or at several locations, including at PA branch take-offs.

Pathophysiology

A stenotic pulmonary valve obstructs the blood flow from the RV to the pulmonary arteries necessitating an increase in RV pressure to maintain cardiac output. This increase in RV pressure is much more marked during exercise and proportional to the severity of stenosis. The increased pressure load results in concentric right ventricular hypertrophy and a less compliant RV. The longer the RV stays exposed to increased pressure load, secondary infundibular hypertrophy could develop ending with more severe obstruction. However, higher RV systolic pressures in such cases distend the infundibulum and cardiac output is maintained. Sudden relief of obstruction in such cases might paradoxically increase infundibular narrowing resulting in a phenomenon called “right ventricular suicide”. An interatrial communication, either an atrial septal defect or probe patent foramen ovale is commonly seen in patients (about 75%) with pulmonary stenosis. As long as the right atrial pressure and RV distensibility are normal, a left to right shunt occurs and might potentiate the physical signs of pulmonary stenosis due to increased flow. As the severity of stenosis increases right ventricular compliance decreases and a right to left shunt develops through the interatrial communication causing more cyanosis.

Natural History

The natural course of patients with pulmonary valve stenosis depends on the severity of the defect and the age at initial presentation. In the neonate with critical PS, presentation is nearly always within the first weeks of life with severe cyanosis. All neonates in whom severe hypoxia develops die without treatment, although some may live for a few months [6]. Mild or moderate PS if not associated with other defects mostly shows a benign course with no major clinical symptoms.

- **Mild valvar PS (gradient <40 mmHg)**—Mild valvar PS is generally benign, and in patients older than 1 or 2 years of age, usually does not progress to more serious disease [7].
- **Moderate valvar PS (gradient 40–60 mmHg)**—Moderate PS may develop to more progressive RVOT obstruction over time [6, 8]. According to a natural history study, 20% of patients with moderate PS ultimately required surgical correction [8]. Many children would have the same life expectancies as that of the general population. But some patients may develop exercise intolerance and fatigue after the second decade of life due to limitation of RV cardiac output.
- **Severe valvar PS (gradient >60 mmHg)**—Severe valvar disease progresses during childhood and these patients show increased RV end diastolic pressure, and in some patients RV hypertrophy, which eventually results into irreversible RV dysfunction if left untreated [9].

Clinical Manifestations

The presentation and clinical manifestations depend on the age, severity of the obstruction and associated cardiac defects. Symptoms occur at a variable valve gradient, but patients with a peak gradient of less than 25 mmHg usually are asymptomatic.

Symptoms

- Fatigue, dyspnea, chest pain, and syncope

Signs

- Cyanosis, clubbing
- The jugular venous pressure reveals an augmented *a* wave
- An ejection systolic murmur best audible in the second intercostal space at the left sternal border and accompanied by a thrill
- There is a normal first heart sound, wide-splitting (not fixed) of the second heart sound with a soft pulmonary component (in severe stenosis)

Diagnostic Evaluation

The diagnosis of PS is usually suspected based on a cardiac examination that identifies the distinctive characteristics of PS (normal first sound accompanied by an audible click, a split second sound, and a systolic ejection murmur at the second left intercostal space). ECG, pulse oximetry and chest-X-ray provide indirect information. Echocardiography is the gold standard for diagnosis and provides both anatomical and functional data including the pressure gradients which are used for estimation of severity of PS. Cardiac computed tomography and magnetic resonance imaging are increasingly being used for anatomic evaluation, functional assessment, and pathologic diagnosis of conditions of the pulmonary valve. Cardiac catheterization is most commonly reserved for catheter-based treatment after diagnosis is confirmed by echocardiography.

Indications for Treatment

Mild pulmonary stenosis (gradient <40 mmHg) is a benign condition which does not require any intervention and can be followed with an echocardiogram every few years. Recent ACC/AHA adult congenital heart disease guidelines for intervention in patients with pulmonic stenosis are summarized below [11]:

- For asymptomatic patients with a domed pulmonic valve and peak instantaneous Doppler gradient >60 mmHg or a mean Doppler gradient >40 mmHg (in association with < moderate pulmonic valve regurgitation), balloon valvotomy is recommended.
- For symptomatic patients with a domed pulmonic valve and peak instantaneous Doppler gradient >50 mmHg or a mean Doppler gradient >30 mmHg (in association with < moderate pulmonic valve regurgitation), balloon valvotomy is recommended.
- Surgical therapy is recommended for patients with severe pulmonic stenosis and an associated hypoplastic pulmonary annulus, severe pulmonary regurgitation, subvalvular pulmonic stenosis, or supravalvular pulmonic stenosis. Surgery is also preferred for most dysplastic valves and when there is associated severe tricuspid regurgitation, the need for a surgical Maze procedure or other cardiac surgical procedure that warrants operative intervention.

PS might be associated with main pulmonary artery aneurysms. There are no definite indications for intervening on an asymptomatic dilated pulmonary artery, as these are low pressure aneurysms with an extremely low risk of dissection or rupture. Repair for evidence of symptomatic compression of neighboring structures and repair at the time of valve replacement are reasonable approaches [12].

Management

The goal is to relieve obstruction without significant pulmonary regurgitation or residual gradient. Currently this is most often achieved with catheter-based interventions; with surgery reserved for failed catheter cases, multi-level obstructions, complex cases or need for additional source of pulmonary blood flow. As the outcome of balloon pulmonary valvotomy (BPV) has been mostly favorable, the need for surgery is becoming uncommon [2].

- Neonates with critical PS require urgent intervention
- In stable patients, the choice between intervention and conservative management is largely based on the severity of PS
- When intervention is indicated, BPV is generally the procedure of choice, if not possible, open surgical valvotomy is indicated
- However, surgical correction may be required in some cases (e.g., supravalvar and subvalvar PS), and some patients with dysplastic pulmonary valves and a hypoplastic annulus or main pulmonary artery

Surgical Techniques

Traditionally surgical treatment was considered the gold standard for PS before the introduction of BPV [13]. The surgical approach evolved from closed valvotomy, first performed in 1948 by Brock, to open valvotomy using inflow occlusion and finally, open valvotomy with cardiopulmonary bypass [14]. With the latter technique, the extent of surgery can be adapted to the needs of the individual patient and can vary from a simple commissurotomy, to a complete RVOT reconstruction with a transannular patch or homograft and even pulmonary valve replacement [15]. Isolated pulmonary valve stenosis is no longer an anomaly that is treated surgically. Balloon dilation at interventional catheterization is highly successful in managing the overwhelming majority of these children, but often leaves behind a partly stenotic and/or regurgitant valve that necessitates regular follow up and, not uncommonly, future interventions [16]. Treatment of this congenital defect with either balloon valvotomy or surgical valvotomy is associated with low morbidity and mortality and excellent long-term outcomes. Surgical pulmonary valvotomy may be performed with an open technique using cardiopulmonary bypass or more rarely through a closed transventricular approach called closed pulmonary valvotomy.

Valvotomy and/or Valvectomy on Cardiopulmonary Bypass

Exposure for open pulmonary valvotomy is obtained through a median sternotomy. After heparinization, an aortic cannula is placed in the ascending aorta, and bicaval cannulation is performed. Patent ductus arteriosus is ligated or snared at the initiation of cardiopulmonary bypass. The procedure may be performed with or without a cross-clamp and cardioplegic arrest. In case an interatrial level communication is present, it is usually left open if elevated right atrial pressure due to poor RV compliance is expected. A longitudinal pulmonary arteriotomy is performed above the level of the valve commissures. The stenotic valve is inspected, and the fused commissures are identified and carefully incised with an 11 scalpel blade. The incisions should extend to the annulus. Any valvar adhesions to the pulmonary arterial wall are sharply incised. Free edges of leaflets are shaved to remove thickened valve tissue or dense scarring on the leaflets. Dysplastic portions of the valve may require excision. The goal is as complete as possible relief of obstruction with preservation of leaflet function. The infundibulum is then inspected through the valve for any residual subvalvular stenosis. Sharp infundibular resection through the valve should be performed if necessary. Rarely, a ventriculotomy is required with an infundibular or transannular patch closure. If a small annulus is present, a Hegar dilator may be used to size the valve annulus. The need for a transannular patch can be determined based on this measurement. If there is supravalvular hypoplasia, a pericardial patch is used to close the incision in the pulmonary artery from the annulus to the base of the left pulmonary artery. The arteriotomy is otherwise closed with a running polypropylene suture. Measurements of pressure in the right ventricle and the main pulmonary artery will document any residual gradient and should be performed before decannulation. Intraoperative transesophageal echocardiography is used to assess any residual gradient or pulmonary valve insufficiency.

Off-Pump Closed Valvotomy

A median sternotomy is done, and a purse string of 4-0 prolene suture is placed on the anterior aspect of the right ventricle just below the infundibulum. A 14-gauge angiocatheter with a pressure transducer is first introduced through the right ventricle into the pulmonary artery. Hegar dilators of progressively larger sizes (up to 7 or 8 mm) are then introduced across the valve. If the membrane does not dilate easily, a long vascular clamp can be passed through the purse string and right ventricle to disrupt the valve membrane. We now prefer the use of a balloon dilation catheter with a balloon, 1–2 mm larger in diameter than the annulus of the pulmonary artery. The balloon can be positioned by measurement and by palpation. A needle pressure transducer is then used to assess the remaining gradient across the valve. After adequate dilation is achieved, the purse string is tied, and an additional reinforcing suture is placed in the ventricular epicardium.

Postoperative Management

As the distending force generated by the obstruction has been removed following an effective valvotomy, it is important to maintain an adequate preload to avoid collapse of the hypoplastic and non-compliant RV cavity. Adequate systemic pressure should be maintained to ensure effective coronary perfusion to the RV as this flow depends on the pressure difference between aorta and RV intracavitary pressure. Use of high dose inotropes should be cautioned as they may impair the diastolic function and increase the residual obstruction. Phosphodiesterase inhibitors may improve diastolic function and may decrease the pulmonary vascular resistance. Tachycardia is detrimental as it impairs the filling of non-compliant RV and should be aggressively managed. In neonates with inadequate antegrade pulmonary blood flow with persistent cyanosis following an adequate pulmonary valvotomy either with a catheter-based or surgical approach an alternative source of pulmonary blood flow may be necessary. This could either be achieved with keeping ductus open with extended PGE therapy, ductal stenting or a modified Blalock-Taussig shunt.

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Truncus Arteriosus

98

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High Yield Facts

- Truncus arteriosus (TA) is a rare congenital cardiac anomaly, accounting for 0.4–4% of all congenital cardiac anomalies.
- A subarterial ventricular septal defect (VSD) due to the absence of the conal septum is nearly always present and is generally unrestrictive.
- The truncal valve straddles the VSD with slight preference towards the right ventricle.
- The truncal valve is tricuspid, quadricuspid, and rarely bicuspid in 70%, 25%, and 5% of the cases respectively.
- Interrupted aortic arch is seen in 10–20% of cases and is generally a Type B interruption between the left common carotid and left subclavian arteries.
- It is a complete mixing lesion at the common trunk and the VSD.
- Early mortality is from intractable congestive heart failure with a 40% 1-month mortality.
- The first successful intracardiac repair was performed in 1962.
- Contemporary approach is full correction at the time of diagnosis (ideally neonatal) unless inoperable due to pulmonary vascular obstructive disease.
- Significant truncal valve stenosis or regurgitation is present in about 25% of the cases.
- Operative mortality is around 5% but is higher for complex forms of TA.
- Actuarial survival among all hospital survivors is 90% at 5 years, 85% at 10 years, and 83% at 15 years with majority having excellent functional status.

Introduction

Truncus arteriosus (TA) is a rare congenital cardiac anomaly, accounting for 0.4–4% of all congenital cardiac anomalies. It was first described in 1798 but morphologic criteria to correctly define the anomaly was first proposed by Lev and Saphir in 1942 [1].

Morphology

TA is part of the conotruncal anomalies, caused by abnormal septation of the conotruncus. It is characterized by a single arterial trunk arising from the heart with a single semilunar valve, giving rise to both the great vessels and the coronary arteries.

A subarterial ventricular septal defect (VSD) due to the absence of the conal septum is nearly always present and is generally unrestrictive. Superiorly the VSD is bound by the truncal valve and inferiorly by septal band limbs. The conduction system is remote from the VSD unless the posterior limb of the septal band is deficient, in which case the VSD will extend into the perimembranous and inlet areas placing the postero-inferior region of the VSD in proximity of the conduction system. The truncal valve straddles the VSD with slight preference towards the right ventricle.

The truncal valve is tricuspid, quadricuspid, and rarely bicuspid in 70%, 25%, and 5% of the cases respectively. It can be regurgitant due to leaflet prolapse and annular dilation or stenotic from commissural fusion. Moderate or greater insufficiency is seen in about 25% of the cases. Mild stenosis is commonly seen due to the combined systemic and pulmonary

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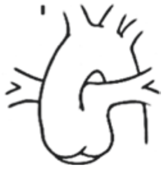
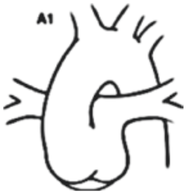
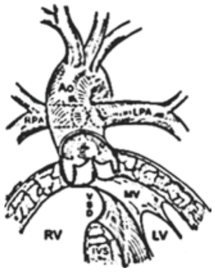
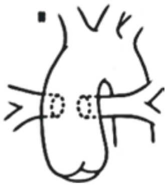
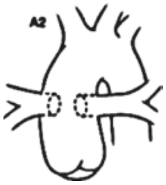
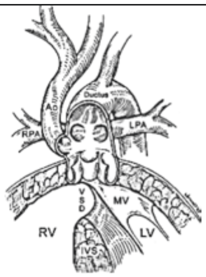
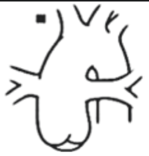
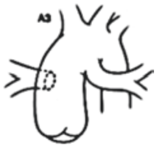
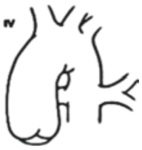
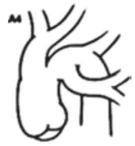
output passing through the truncal valve. However, gradient greater than 30 mmHg is seen in 4–7% of cases and can persists after complete repair [2].

A ductus arteriosus is generally absent unless there is an aortic arch interruption in which case it is always present to maintain systemic perfusion [3].

Various anomalies of the coronary arteries have been described of which a high rising left coronary artery is important as it can be potentially damaged during the separation of the pulmonary arteries from the truncal artery. Rare cases of coronary arteries arising from the branch pulmonary arteries (PAs) have been described [4].

Fig. 98.1 Classification systems of truncus arteriosus. Van Praagh$^{\alpha}$ types are further divided into A and B by the presence or absence of a ventricular septal defect (VSD) respectively. *Hemitruncus*$^{\$}$ should be differentiated from a condition with aberrant origin of the right pulmonary artery (PA) from the ascending aorta and the left PA from the right ventricular outflow tract RVOT and presence of two separate semilunar valves. *Pseudo Truncus*$^{\$\$}$ should be included in pulmonary atresia with VSD anomalies rather than being part of the truncus arteriosus (TA) spectrum

Collet -Edwards	Van Praagh$^{\alpha}$	Chicago
 **Type I**-Presence of a main pulmonary arterial trunk giving rise to the branch PAs	 **Type A1**-Presence of a main pulmonary arterial trunk giving rise to the branch PAs	 **Aortic dominant**- Truncus continues as the ascending aorta after giving rise to PAs
 **Type II**- Absence of the main pulmonary trunk with the branch PAs directly arising from the truncus	 **Type A2**- Absence of the main pulmonary trunk with the branch PAs directly arising from the truncus	 **Pulmonary dominant**- Truncus continues as the ductus after giving rise to ascending aorta. The arch is interrupted.
 **Type III**- Similar to Type II except the branch PAs arise far apart from the truncus	 **Type A3**- Only one branch PA arises from the common trunk "*Hemitruncus*"$^{\$}$. The other branch usually arises from the ductus	
 **Type IV**- *Pseudo Truncus*$^{\$\$}$	 **Type A4**- Hypoplasia or interruption of the aortic arch with TA	

Interrupted aortic arch (IAA) is seen in 10–20% of cases and is generally a Type B interruption between the left common carotid and left subclavian arteries. Right aortic arch is present in 20% of the cases.

As with other conotruncal anomalies, TA is associated with DiGeorge syndrome [5].

Classification

There are three well described classification systems (Fig. 98.1) namely Collet-Edwards, Van Praagh and Chicago classification [6].

Natural History

Early mortality is from intractable congestive heart failure with a 40% 1-month mortality. Few patients (10%) who survive to infancy will eventually succumb to pulmonary vascular obstructive disease.

Pathophysiology

It is a complete mixing lesion at the common trunk and the VSD. Pulmonary blood flow is primarily determined by pulmonary vascular resistance (PVR) unless there is branch PA obstruction or systemic obstruction. Complete mixing causes saturations to be around 85–90%. With the drop in the PVR in early weeks of life, pulmonary blood flow increases, leading to congestive heart failure. The combination of increased pulmonary blood flow and cyanosis leads to early development of obstructive pulmonary vascular disease. Associated truncal valve pathology can worsen the clinical condition. Truncal valve regurgitation worsens the congestive heart failure due to volume loading of the ventricle and exacerbates coronary steal by enhancing diastolic runoff. Truncal stenosis causes additional pressure overload of a volume loaded ventricle.

Diagnosis

Diagnosis is by a transthoracic echocardiogram. It is useful in delineating the anatomy of the VSD and anatomy and function of the truncal valve. Anatomy of the aortic arch and the branch PAs can be better imaged with magnetic resonance imaging or computed tomography scan. Endoluminal views particularly delineating the origin of the coronary arteries and three dimensions reconstruction of the arterial branch vessels can help with operation [4]. Cardiac catherization is not required unless obstructive pulmonary arterial disease is suspected due to delayed presentation.

Treatment

TA is a surgical disease unless inoperable due to advanced pulmonary vascular obstructive disease. Historically, the repair was either palliative branch PA banding or a multistep process with an initial PA banding followed by complete intracardiac correction. The first successful intracardiac repair was performed in 1962 [7]. Contemporary approach is full correction at the time of diagnosis (ideally neonatal) unless inoperable as previously alluded.

The defect is repaired via a median sternotomy. Simple forms of TA are repaired using full flow moderate hypothermic cardiopulmonary bypass (CPB). Associated IAA will require deep hypothermia. Drainage is usually bi-caval with arterial return being the distal aorta at the base of the innominate artery. Placement of the aortic cannula is crucial as it facilitates the easy and safe separation of the arterial trunks. In case of IAA, the brachiocephalic artery can be directly cannulated in order to provide selective cerebral perfusion and distal aortic perfusion is maintained via the truncus with occlusion of the branch PAs or by directly cannulating the distal ductus with an additional arterial cannula. Suturing a “Chimney graft” to the brachiocephalic artery for arterial return is another very useful technique. It not only helps with very distal aortic control thus helping with the ease and safety of separating the PAs from the truncus but also in case of an IAA can help with selective cerebral perfusion. The left heart is vented via the right superior pulmonary vein.

Branch PAs are mobilized and snared to prevent pulmonary run-off of the arterial perfusate on initiation of CPB.

Myocardial protection is by antegrade cardioplegia unless there is severe truncal valve insufficiency, in which case either retrograde or direct ostial antegrade cardioplegia is used.

The key step is safe separation of the common pulmonary trunk if present or the branch PAs from the truncal artery without injuring particularly the left coronary ostia and the truncal valve. The PA usually arises from the left-posterior aspect of the truncal artery and can be very close to the left coronary orifice especially when it arises high. The process can be facilitated by incising the truncal artery several centimeters distal to the sinutubular junction and performing an internal inspection of the orifices before separating the pulmonary trunk.

When a common pulmonary trunk is present, the excision is simple. However, when the branch pulmonary arteries arise widely apart on the truncal artery or are staggered in origin, then either a portion of the truncal wall connecting the branches or buttons incorporating portions of the truncal wall are included during the separation process.

The resultant defect in the truncus is repaired primarily or patched depending upon the extent of the defect.

An alternative technique is to completely transect the truncus just distal to the sinutubular junction and the upper margin of the site of origin of the PAs. The PAs can then be completely harvested from the truncus with constant visualization of the truncal valve and coronary ostia. The resultant defect is patched and the aorta reconstructed back in an end to end fashion.

A limited infundibulotomy is performed in an area devoid of a major conal branch or a crossing left anterior descending artery. Care must be taken to avoid injuring the truncal valve on superior extension of the ventriculotomy.

The outlet VSD is closed with a patch. If there is a membranous or inlet extension, care must be taken to avoid the conduction system in the posterior-inferior aspect of the defect. The superior extent of the patch is secured by sutures brought from the epicardial aspect of the ventriculotomy on to the patch to avoid injuring the truncal valve and to prevent crowding of the left ventricular outflow tract. Rarely, when the VSD is small, it is enlarged in the antero-superior aspect to prevent left ventricular outflow tract obstruction.

Right ventricle to PA continuity is established with a variety of conduits. These range from allografts to xenografts such as bovine jugular vein and valved PTFE conduits. Latter are useful when there is a limited availability of allografts and concerns for immune sensitization. While the aortic allograft can provide better fit due to its length and curvature, a pulmonary allograft has a better tissue match especially when the branch PAs are to be incorporated into the reconstruction. The valve in the allograft is positioned distally than in a native position to avoid sternal compression causing distortion and insufficiency. With allografts, the proximal anastomosis may need to be supplemented with a hood in order to contour the conduit into the right ventricular outflow tract.

Alternative techniques of repair include avoid using an RV to PA conduit with a potential advantage of avoiding the need for conduit replacement. The pulmonary bifurcation is directly anastomosed to the ventriculotomy to form the back wall (can be bridged with LA appendage if distance is large) and the front wall reconstructed with (monocusp) or without a valved patch [8].

Another technique involves not separating the pulmonary trunk but patch closing its opening in the truncus like an aortopulmonary window. Care should be taken to avoid the left coronary ostium in the inferior aspect of the defect. This technique causes less distortion of the branch PAs but is best suited when there is a common PA trunk [8, 9]. The RV to PA continuity is reestablished with a conduit or by bringing the PA bifurcation on to the ventriculotomy as previously described.

A valved conduit facilitates an easier postoperative course with a survival benefit since the combination of a reactive pulmonary vascular bed, depressed RV function from a ventriculotomy, and free pulmonary insufficiency leads to marginal RV hemodynamics. However, it is does commit to recurrent reinterventions due to early conduit failure from somatic growth with late failure due to structural degeneration.

Monocusp reconstruction can provide a middle ground of an easier postoperative course due to immediate PA competency despite later failure, yet with potential for growth due to non-circumferential nature of the reconstruction.

Repair of the IAA is performed with cannulation and perfusion strategy as previously described. The arch reconstruction can be performed by a direct proximal descending aorta to the distal ascending aorta end to side anastomosis or the back and superior wall can be constructed by bringing the ascending and descending aorta together and the anterior and inferior wall reconstructed with a patch such as a pulmonary homograft. The patch technique helps avoid bowstringing of the anastomosis on the left bronchus. Concomitant repair of IAA with TA has a variable effect on mortality with some studies showing no effect to others showing an increased mortality particularly in the context of truncal valve intervention [10].

Significant truncal valve stenosis or regurgitation is present in about 25% of the cases. A conservative approach is recommended at primary surgery as both improve after corrective surgery, especially given that concomitant valve surgery can increase mortality. However, patients who have omission of valve repair but require it subsequently as a rescue measure during the same hospitalization have a higher mortality [10]. Thus, proper patient selection is important. Abnormal number of valve leaflets and severe dysplasia is predictive of the need for a valve intervention [11]. Valve regurgitation up to moderate degree and valve gradients up to 30 mmHg should be tolerated because of a mortality benefit despite predisposing to need for valve reintervention later. Repair is preferred as it has a mortality benefit over replacement especially at primary surgery [12]. Repair techniques include excision of the redundant prolapsing leaflet with or without coronary artery transfer depending on the location of the leaflet, valvuloplasty of the prolapsing leaflet to the adjacent normal leaflets, commisuroplasty and annuloplasty. Abnormal valve leaflet resection tends to be more durable than valvuloplasty [13]. Replacement techniques involve prosthetic valve replacement without or without annular enlargement into the VSD or root replacement with an allograft.

Post-operative Management

Key issues include right ventricular dysfunction and pulmonary hypertensive crises. Reactive pulmonary hypertensive crises is likely if the repair is performed outside the neonatal or early infancy period. It is managed by avoiding hypoxia, hypercarbia, acidosis, and by using paralytics and pulmonary vasodilators like inhaled nitric oxide or sildenafil. A transthoracic PA line may help in the management. The RV is supported with inotropes and a left atrial line can help delineate right versus biventricular dysfunction. Serum ionized calcium is closely followed in patients with DiGeorge syndrome.

Outcomes

Operative mortality is around 5% but is higher for complex forms of TA. Actuarial survival among all hospital survivors is 90% at 5 years, 85% at 10 years, and 83% at 15 years with majority having excellent functional status. Conduit replacement is almost inevitably necessary especially if a small sized conduit was used during the initial repair. Patients with truncal valve insufficiency at the primary operation are predisposed to valve reinterventions [14].

Conclusion

Most patients with truncus arteriosus are symptomatic in the neonatal period with cyanosis and/or congestive heart failure and undergo complete repair in the first few weeks of life. The physiologic basis for improved outcomes with earlier repair is the avoidance of damaging sequelae of pulmonary overcirculation and heart failure. Data show that baseline mean pulmonary artery pressure is lower in infants undergoing earlier repair. Improved operative outcomes also have been achieved with aggressive truncal valve repair versus replacement in the presence of truncal valve dysfunction, right ventricular outflow tract reconstructive techniques that are patient anatomy-specific, and use of regional perfusion techniques for repair of associated IAA.

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Transposition of the Great Arteries

99

Erik L. Frandsen and Matthew D. Files

High Yield Facts

- In transposition of the great arteries (TGA), the aorta arises from the right ventricle and the pulmonary artery arises from the left ventricle, creating an unstable situation where the systemic and pulmonary circulations run in-parallel as opposed to in-series.
- Pre-operative survival is dependent on adequate mixing at the atrial, ventricular, or great artery level.
- The majority of the cardiac output of the right and left ventricles is inadequate and pre-operative stabilization focuses on maximizing inter-circulatory mixing.
- Focused anatomic survey of atrial shunting, presence of ventricular septal defects, outflow tract obstruction, and coronary arterial pattern determines surgical strategy.
- Survival after arterial switch procedure is excellent, with >95% survival at 20 years.
- Left ventricular outflow tract obstruction requires consideration of Rastelli, Nikaidoh, or REV procedures.
- Lifelong surveillance for coronary artery insufficiency, branch pulmonary artery stenosis, and neo-aortic root dilation are required.
- Patients are at high risk of multiple neurodevelopmental deficits.

Introduction

Transposition of the great arteries (TGA) refers to hearts with concordant atrioventricular connections but discordant ventriculoarterial connections. In this lesion, the aorta arises from the right ventricle (RV) and the pulmonary artery arises from the left ventricle (LV). This results from abnormal rotation and septation of the truncus arteriosus in early cardiovascular development. Pulmonary and systemic circulations run in parallel as opposed to in series. Thus, adequate mixing between these circulations is required for survival. Detailed perioperative imaging, attention to associated lesions, and comprehension of the physiology are imperative to medical and surgical management. Long-term outcomes are excellent, however life-long surveillance is necessary.

Epidemiology

TGA represents 5–7% of all congenital heart disease, yet is one of the most frequent causes of newborn cyanosis. The prevalence is 0.2–0.3 per 1000 live births, with a greater than twofold male predominance [1]. There are currently no known associated fetal environmental risk factors.

Physiology

In this chapter TGA will refer to hearts with isolated ventriculoarterial discordance, meaning that the aorta is connected to an anatomical RV and the pulmonary artery is connected to an anatomical LV. Patients with discordant atrioventricular and ventriculoarterial connections ("L-" or "congenitally corrected" TGA), univentricular hearts, and forms of double-outlet RV with transposed great vessels will be excluded.

In TGA, the postnatal circulation is dependent on some form of shunting at the atrial, ventricular, or great artery level to be compatible with life. Effective pulmonary blood

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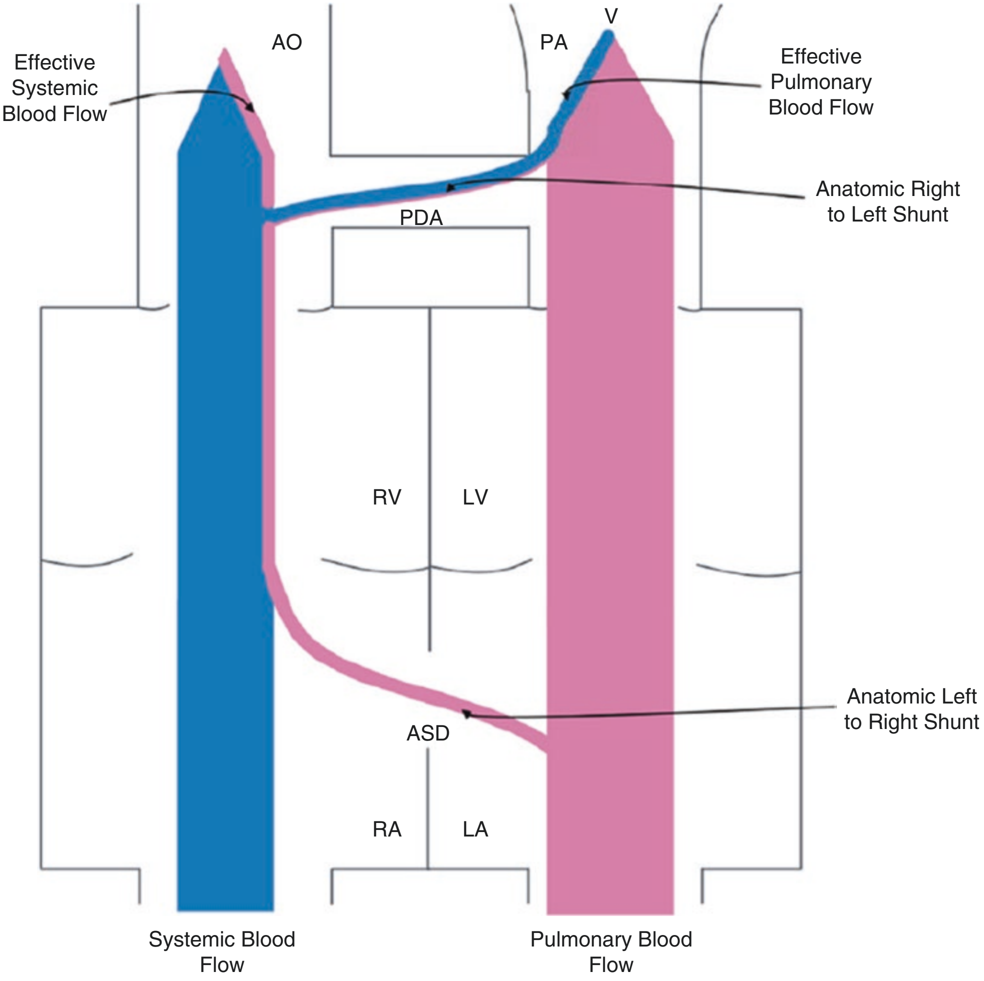

Fig. 99.1 Schematic demonstrating the circulation of transposition of the great arteries with intact ventricular septum, with intercirculatory mixing at the atrial and great artery levels. The majority of the systemic and pulmonary blood flow is recirculated within the parallel circulations and is ineffective. An anatomical left-to-right shunt is seen at the atrial level, which ultimately enters the systemic circulation as effective, oxygenated blood flow. An equal volume passes from the aorta to the pulmonary artery as effective pulmonary blood flow. As seen in the shunt at the PDA, a small portion of the anatomical shunt is derived from the pulmonary circulation; thus, the anatomical shunt may be greater than the effective pulmonary blood flow. *Abbreviations*: *AO* aorta, *ASD* atrial septal defect, *LA* left atrium, *LV* left ventricle, *PA* pulmonary artery, *PDA* patent ductus arteriosus, *RA* right atrium, *RV* right ventricle. (Reprinted with permission of SAGE Publications from Files M, Arya B. *Preoperative Physiology, Imaging, and Management of Transposition of the Great Arteries*. Seminars in Cardiothoracic and Vascular Anesthesia, 2015, https://doi.org/10.1177/1089253215581851)

flow represents desaturated systemic venous blood that reaches the pulmonary vascular bed. Likewise, the effective systemic blood flow represents the oxygen-rich pulmonary venous blood that reaches the systemic circulation. This concept is illustrated in Fig. 99.1. Although the cardiac output of each ventricle is typically increased 2–4 times the normal, the majority of this cardiac output is ineffective [2].

Presence of associated lesions, such as ventricular septal defect (VSD) or outflow tract obstruction influences the physiology and surgical strategy. TGA with intact ventricular septum (TGA-IVS) represents the most common variant, accounting for 50% of TGA [3]. In TGA-IVS, the physiology is dependent on the size and direction of shunting at the atrial and great artery level. The right ventricular and right atrial pressures are increased, which often is sufficient to keep the foramen ovale open with bidirectional shunting. Flow from right to left across the patent foramen ovale (PFO) results in effective pulmonary blood flow (deoxygenated blood entering the pulmonary bed). The size of shunt through the PFO is variable, however and depends on the degree of shunting at the great artery level. Immediately after birth, shunting through the patent ductus arteriosus (PDA) is typically pulmonary to aorta in systole and reversed in diastole due to physiologic elevated pulmonary vascular resistance. This may account for reverse differential cyanosis, which refers to higher saturations in the lower extremities than in the arms. This is a unique finding found nearly exclusively in TGA and represents effective systemic blood flow (oxygenated blood entering the systemic circulation) [4]. As the postnatal pulmonary vascular resistance falls in the absence of persistent pulmonary hypertension or a preductal coarctation, the majority of shunting through the PDA will become aorta to pulmonary artery. As more blood returns to the left atrium, left atrial pressures increase, which forces the flap of the PFO shut, which may eliminate this important source of atrial mixing. With closure of the PFO, profound hypoxemia and hypoxia can develop with saturations <70%, PaO_2 <35 mmHg, and ensuing acidosis.

A VSD is found in approximately 40% with TGA, however a third of these are small and not functionally significant [5]. For patients with a large unrestricted VSD, this allows mixing. As pulmonary vascular resistance drops through the neonatal period, this may set up significant pulmonary overcirculation, resulting in signs and symptoms of congestive heart failure including feeding intolerance, failure to thrive, respiratory distress, and hepatomegaly.

Left ventricular outflow tract (LVOT) obstruction is an important consideration in the postnatal physiology and may influence the surgical management considerably, as discussed later. Around 10% will have "true" LVOT obstruction consisting of muscle bundles or fibrous tissue, the majority of which occurs with a VSD [5]. LVOT obstruction may also be acquired in infants with TGA-IVS who do not undergo early repair. In these instances, as the left ventricular pressure falls in response to decreasing pulmonary vascular resistance, the interventricular septum bulges from the pressure loaded RV into the LVOT, causing dynamic obstruction. TGA with VSD and LVOT obstruction sets up large-volume LV to RV shunting. The amount of effective blood flow depends on the degree of shunting at the level of the atrium and/or the PDA.

Right ventricular outflow tract (RVOT) obstruction is less common, occurring in less than 10% of cases. In these instances, careful evaluation of downstream structures is necessary due to increased risk of aortic arch hypoplasia or coarctation.

Preoperative Imaging

TGA remains one of the most difficult congenital heart diseases to diagnosis prenatally because of a relatively normal appearance in the 4-chamber view. Detection rates are low, ranging between 3% and 41% [6–11]. Predicting whether the atrial septal defect (ASD) or PFO will provide enough mixing postnatally is difficult. Thus, current guidelines recommend that all fetuses with TGA are delivered at a hospital that can manage the hypoxia and hemodynamic compromise associated with a restrictive ASD [12].

Preoperative imaging is vital to surgical planning and preoperative management. Particular attention must be paid towards the following:

- Spatial relationship between the semilunar valves and their commissural alignment, which is important for planning coronary transfer during surgical repair.
- Evidence of restriction at the atrial septum that may necessitate balloon atrial septostomy.
- The presence or absence of a VSD.
- Evidence of outflow tract obstruction.
- PDA size, location, and shunting characteristics.
- Coronary artery anatomy.

Special mention of coronary artery anatomy is necessary, as early mortality after the arterial switch operation is almost always a result of difficulty with coronary artery translocation [13–15]. Specifically, intramural coronary course or single coronary artery pattern are associated with increased risk of death [15].

In TGA, the aortic sinuses are named based on their relationship to the pulmonary root. There are two pulmonary "facing" sinuses and one "nonfacing" sinus. Depending on the spacial relationship of the great arteries, the facing sinus are named left-anterior facing (left-facing or anterior-facing in the anterior-posterior or side-by-side relationships, respectively) or right-posterior facing (right-facing or posterior facing in the anterior-posterior or side-by-side relationships, respectively) (Fig. 99.2) [16].

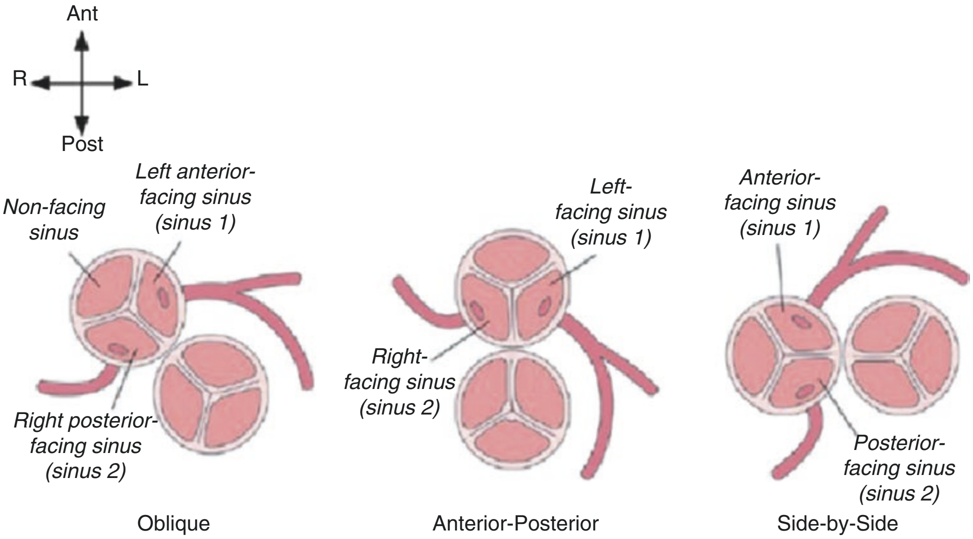
Ant
R
L
Post
Non-facing sinus
Left anterior-facing sinus (sinus 1)
Right posterior-facing sinus (sinus 2)
Oblique
Left-facing sinus (sinus 1)
Right-facing sinus (sinus 2)
Anterior-Posterior
Anterior-facing sinus (sinus 1)
Posterior-facing sinus (sinus 2)
Side-by-Side

Fig. 99.2 Designation of the aortic sinuses based on the parasternal echocardiographic view. (Copyrighted image from: Lai et al., Echocardiography in Pediatric and Congenital Heart Disease)

In the majority of patients, the coronary arteries arise from the aortic sinuses facing the pulmonary root. The most common or "usual" coronary artery pattern in TGA involves the left anterior descending and left circumflex arteries arising from the left-facing sinus and the right coronary artery arising from the right-facing sinus. The second most common pattern involves left circumflex artery arising from the right facing sinus, and multiple variants beyond that. Generally, an intramural coronary artery originates from the pulmonary facing sinus with its proximal course running within the wall of the aorta.

Preoperative Management

Newborns with TGA are classically not in significant respiratory distress and frequently will be comfortable with fairly severe cyanosis and only mild tachypnea. Additionally, the presence of reverse differential cyanosis is unique to TGA and can be sufficient to make the provisional diagnosis. As in all cyanotic heart disease presenting in the newborn period, initiation of prostaglandin E1 (PGE) is imperative. After the diagnosis of TGA is made, the risks and benefits of balloon atrial septostomy, continuation of PGE, and surgical timing must be weighed.

Balloon Atrial Septostomy

Balloon atrial septostomy (BAS) involves the percutaneous advancement of a balloon-tipped catheter across the atrial septum into the left atrium, inflation of the balloon, and retraction across the septum, which creates a larger defect and thus encourages greater mixing between the systemic and pulmonary circulations. There is no evidence based criteria for performance of BAS for infants with TGA, with reported incidences ranging between 20% and 75% [17]. Some use criteria of PaO_2 <30 mmHg and/or a size of the patent foramen ovale <3 mm as indications for performing a BAS. The benefits of acute and dramatic improvement in saturations must be weighed against the risk of vascular trauma, arrhythmias, and rare complications such as atrial perforation and avulsion of the inferior vena cava.

Prostaglandin E1

Prostaglandin E1 is a naturally occurring prostaglandin that prevents closure of the ductus arteriosus. PGE usually improves saturations in TGA and should be initiated in any infant with a prenatal diagnosis of TGA. Theoretically, as the net shunts in either direction must equal each other, a shunt from the aorta to the pulmonary artery will be matched by an atrial or ventricular shunt in the opposite direction, thus increasing intercirculatory mixing and effective blood flow. However, large volume aorta to pulmonary artery shunting can lead to left atrial hypertension, which creates pulmonary edema. Additionally, run off from the PDA can decrease overall systemic cardiac output. PGE also has associated apnea, fever, and hypotension as well-recognized side effects. Whether or not a BAS is performed, many infants will continue to need PGE until the time of surgery [18].

Timing of Surgery

Timing of repair is largely center dependent. A recent report from Karamlou et al. lists day of life 6 or 7 as the average time for the arterial switch operation in the United States based on the Society for Thoracic Surgeons Congenital Database [19]. A recent retrospective review supports day of life 3 as the ideal time for ASO, with increasing morbidity if ASO is performed earlier or later [20]. Other reports show success with ASO performed in the first hours of life for neonates with a prenatal diagnosis [21].

Surgical Techniques

Historical Perspective

The management and outcomes of TGA parallels the field of pediatric cardiac surgery itself. Uniformly fatal in childhood, palliative procedures from the 1950s to 1970s offered survival, albeit at a high early and late cost. The first approach to TGA involved rerouting systemic and pulmonary venous blood flow rather than arterial blood flow in what is known as the "atrial switch" operation. The 1950s and 1960s Drs Senning and Mustard devised their atrial switch operations. The Mustard repair consists of baffling systemic venous blood to the morphologic left ventricle through a pants shaped atrial patch, the "legs" of the patch receiving blood from the vena cavae, with the "waist" delivering blood into the left atrium [22]. The atrial switch operation has been largely abandoned for patients with TGA due to late complications including atrial arrhythmias, baffle leaks and obstruction, and failure of the morphological right ventricle subject to chronic systemic loads. In 1975, Dr. Adib Jatene performed the first successful arterial switch operation (ASO) [23]. By switching the great vessels, there is now ventriculoarterial concordance with "normal" physiology.

Arterial Switch Operation

The ASO begins with mobilization of the aorta, proximal arch, and ductus, as well as wide mobilization of the pulmonary arteries, and confirmation of coronary artery pattern. Cannulation and cardioplegic arrest is then undertaken. The initial step is division of the ascending aorta followed by excision of each coronary ostium with an ample amount of sinus of Valsalva tissue, termed "coronary buttons." The proximal portions of the coronary arteries must be mobilized to allow for transfer to the neo-aorta. Next, the pulmonary artery is divided. Techniques vary, however the goal of coronary transfer is to implant the coronary arteries on the neo-aorta, preventing kinking, tension, or distortion that impairs coronary flow [24]. In the presence of coronary artery anomalies (single coronary, coronaries arising from the same sinus, intramural coronaries), different techniques prevail. The neo-pulmonary root, now devoid of "coronary-button" tissue must be reconstructed to maintain circumferential diameter. Once reconstructed, the pulmonary artery must be brought anterior to the ascending aorta prior to connection to the neo-pulmonary root, termed the Lecompte maneuver (Fig. 99.3). The ascending aorta is now connected to the neo-aortic root. Any ventricular and atrial level communications will be closed.

Upon cardiac reperfusion, post-operative imaging by transesophageal echocardiography is necessary to demonstrate adequate coronary flow in addition to assessments of ventricular and valvular function as well as residual atrial and ventricular septal defects. Ventricular dysfunction or significant ectopy should raise concern for coronary insufficiency and should be investigated and treated promptly.

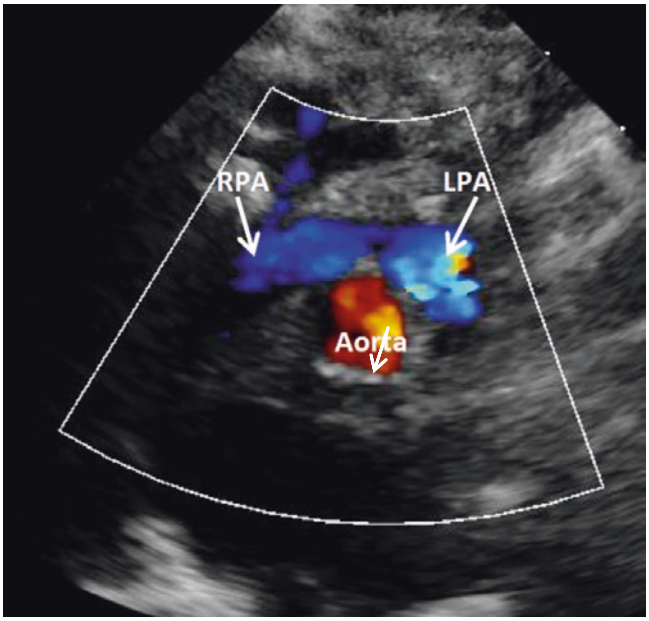

Fig. 99.3 Color Doppler view of the right and left branch pulmonary arteries (RPA and LPA) as they straddle the ascending aorta after the LeCompte maneuver

Post-operative care focuses on managing bleeding, myocardial performance, pulmonary vascular resistance, and lung function. Patients are typically supported with mechanical ventilation, blood product administration, and various combinations of inotropic and vasopressor infusions, as well as inhaled nitric oxide utilized in patients with evidence of elevated pulmonary vascular resistance. In routine, uncomplicated cases, patients can typically be extubated within 24 h.

Presence of Outflow Tract Obstruction

Surgical strategy may need to be altered in the presence of TGA with VSD and outflow tract obstruction. As the pulmonary artery will become the neo-aorta any pulmonary stenosis, particularly subvalvar, will become LVOT obstruction following ASO. As mentioned previously, these patients typically have a VSD [5]. If resection of obstructing subvalvar muscle or fibrous tissue cannot be accomplished intraoperatively, then other surgical procedures may be necessary. Three major operative strategies have been developed over the past four decades.

The Rastelli operation involves directing blood from the LV to the aorta by way of a patch between the VSD and the aortic valve, and establishing continuity between the right ventricle and pulmonary artery with a conduit [25]. This operation requires an adequately sized VSD. Disadvantages include the potential for LVOT obstruction due to a long patch baffle, long-term effects of right ventriculotomy (cardiomyopathy and arrhythmia), and need for subsequent RV to pulmonary artery conduit replacement [24]. The *reparation á l'étage ventriculaire* (REV) procedure is similar to the Rastelli operation in which left ventricular blood is baffled to the aortic valve. The pulmonary arteries are brought in front of the aorta and connected directly to the morphologic right ventricle with a ventriculotomy [26]. A third option is the Nikaidoh operation, which involves mobilizing and excising the native aortic root from the RV, posteriorly translocating the aortic root to the pulmonary annulus, from which the main pulmonary artery has been removed, and reconstructing the RVOT [27]. This surgery creates a wide-open LVOT without the need for a baffle, however is technically difficult, and requires a non-native RV to pulmonary artery connection.

Long-Term Follow Up

Outcomes for ASO are excellent, with operative mortality at experienced center's less than 5%, and long term survival >95% at 20 years [13, 28–31]. Patients with complex coronary patterns (intramural, single coronary) may be at risk for future coronary obstruction, occurring in 5–7% of patients [32–34]. Although coronary obstruction most often occurs in the first 3 months following ASO, silent long-term obstruction also occurs, and initial coronary anatomy should always be considered during long-term follow-up as screening and detection of myocardial ischemia continues to evolve. Neo-pulmonary artery stenosis, branch pulmonary artery stenosis from the LeCompte maneuver, neo-aortic root enlargement, and neo-aortic regurgitation are all common issues and may require re-intervention and require ongoing follow-up [35–37]. Although physical health is typically very good, there is a striking prevalence of mild but widespread neurodevelopmental abnormalities in TGA survivors [38], which are functionally more significant than their residual cardiac disease.

Conclusion

The management of TGA has evolved rapidly and impressively since the introduction of the ASO. Once uniformly fatal, patients with TGA now experience excellent long-term survival. Afforded the luxury of low mortality, we are becoming more aware of the longer term morbidities. Our focus should now transition to early strategies to optimize long-term neurodevelopmental outcomes and continue to build multidisciplinary support for patients as they age.

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Congenitally Corrected Transposition of the Great Arteries

100

Michel N. Ilbawi, Chawki El-Zein, and Luca Vricella

High Yield Facts

- Congenitally corrected transposition of the great arteries (ccTGA) is a rare malformation with an incidence of 0.5% of congenital heart defects.
- Patients with isolated ccTGA have potentially physiologic circulation, hence the term congenitally (not surgically) corrected transposition.
- ccTGA is frequently associated with ventricular septal defect (VSD), pulmonary valvar and subvalvar stenosis and abnormalities of the tricuspid valve.
- In the absence of other malformations, patients with ccTGA are asymptomatic early in life.
- The surgical approach to patients with ccTGA depends on the presence and severity of the associated lesions.
- The traditional surgical approach (physiologic repair) of ccTGA attempts at restoring normal physiology by repairing the associated lesions.
- Physiologic repair fails to address the most serious anatomic abnormality, mainly ventriculoarterial discordance, and results in less than optimal long-term outcomes. Anatomic repair (double switch) incorporates the left ventricle into the systemic circulation.
- Double switch includes an atrial baffle to redirect venous return in combination with either arterial switch or Rastelli operation (if a suitable VSD permits).
- The excellent short-term and intermediate results of the double switch operation and its modifications make it the procedure of choice for the treatment of ccTGA.
- Occasionally, the anatomic peculiarities of ccTGA do not allow straightforward biventricular repair, and univentricular palliation is a reasonable option.

Introduction

Congenitally corrected transposition of the great arteries (ccTGA) is a rare malformation with an incidence of 0.5% of congenital heart defects. Patients with isolated ccTGA have potentially physiologic circulation, hence the term congenitally (not surgically) corrected transposition. This corrected circulation results from atrioventricular and ventriculoarterial discordance. The systemic venous return enters the right atrium and passed through the mitral valve to end into a morphological left ventricle which ejects the blood to the lung through the pulmonary valve and artery. Fully oxygenated pulmonary venous return enters the left atrium, passes through the morphologic tricuspid valve to empty into morphologic

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right ventricle, which pumps blood into the systemic circulation through the aortic valve and aorta. This double pathologic discordance results in a physiologic circulation with a systemic right ventricle [1].

Embryologically, ccTGA results from left sided bend of the cardiac tube (l-loop) and the aorta maintaining continuity with the bulbus cordis, l-transposition [2]. The l-transposition implies that the aortic valve is anterior and the left of the pulmonary valve. However, in cases with situs inversus, the aorta lies to the right of the pulmonary artery (5%). It is common to refer to the pathology as SLL or IDD based on Van Praagh's segmental definition [3]. The three letters refer to the situs solitus (S) vs. Inversus (I), to the ventricular loop dextro (D) vs. levo (L) and to the malposition of the great arteries dextro (D) vs. levo (L). In clinical practice, it is best to specify the atrioventricular and ventriculoarterial connections to avoid confusing this entity with much rarer malformations such as isolated AV discordance, crisscross heart, double outlet from either ventricular chambers or single ventricle with atresia of either pulmonary or aortic valve [4].

Most patients with ccTGA have situs solitus with levocardia. The morphologic right ventricle is left sided and the left ventricle is right sided. In 25% of cases there is dextro or mesocardia with situs solitus. Rarely there is situs inversus with the heart apex pointing to the right.

Surgical Pathology

ccTGA is frequently associated with other lesions. These include ventricular septal defect (VSD), pulmonary valvar and subvalvar stenosis and abnormalities of the tricuspid valve. Rarely (1%) the atria, ventricles and great arteries are anatomically and functionally normal except for their discordant connections.

Ventricular Septal Defect

It is the most common associated cardiac malformation. It is present in 70–85% of cases. Malalignment of the atrial and ventricular septa, characteristic of ccTGA, results in an enlarged pars membranacea. Consequently, most VSDs are perimembraneous. Typically, the defect is large, nonrestrictive, and single. It may extend into the inlet or infundibular septum. It is usually separated from the aortic valve by a subaortic infundibulum of variable length [5]. Rarely the inlet and trabecular septum is completely absent resulting in a single ventricle with a subaortic outlet chamber [6].

Left Ventricular Outflow Tract

The pulmonary outflow tract is wedged deeply between the mitral and tricuspid valve due to malalignment of the septa [7]. This position predisposes to the development of stenosis of the morphologically left ventricular outflow tract in 35–50% of cases, at the subvalvar or valvar level. Obstruction at the level of pulmonary valve is causes by fused and/or thickened dysplastic leaflets. Subvalvar stenosis results from subvalvar fibromuscular ridge, aneurysm of the membraneous septum or tunnel. Accessory mitral valve tissue with or without abnormal chordal attachments to the septum could also be present.

Atrioventricular Valves

Significant number of patients (26%) with ccTGA have a morphologically abnormal dysplastic tricuspid valve. The septal leaflet is most affected. It has shortened and thickened chordae tethering the leaflet to the posterior wall. It is frequently displaced toward the apex of the right ventricle in an "ebstenoid fashion" but without atrialization of the ventricular septum [8]. These pathological changes of the tricuspid valve in combination with progressive annular dilatation (due to shift of the interventricular septum towards the morphologic left ventricle) results in regurgitation that is not readily amendable to valvuloplasty. Straddling of the tricuspid valvar or subvalvar apparatus across a ventricular septal defect, could be present and complicates the surgical repair.

Coronary Arteries

The morphology of the coronary arteries is a mirror image of the normal anatomy [9]. The arteries follow the respective inverted ventricles. The right-sided coronary artery has a left distribution. It arises from an anterior sinus of the aortic valve and divides into an anterior descending artery that follows the outline of the interventricular septum, and a circumflex that follows the atrioventricular groove and supplies multiple marginal vessels. The left sided right coronary arises from a posterior sinus and courses into the left atrial–right ventricular groove to supply the free wall of the morphologic right ventricle (Fig. 100.1).

Conduction System

Malalignment of the atrial and ventricular septum displaces the atrioventricular node (AV) anteriorly and superiorly

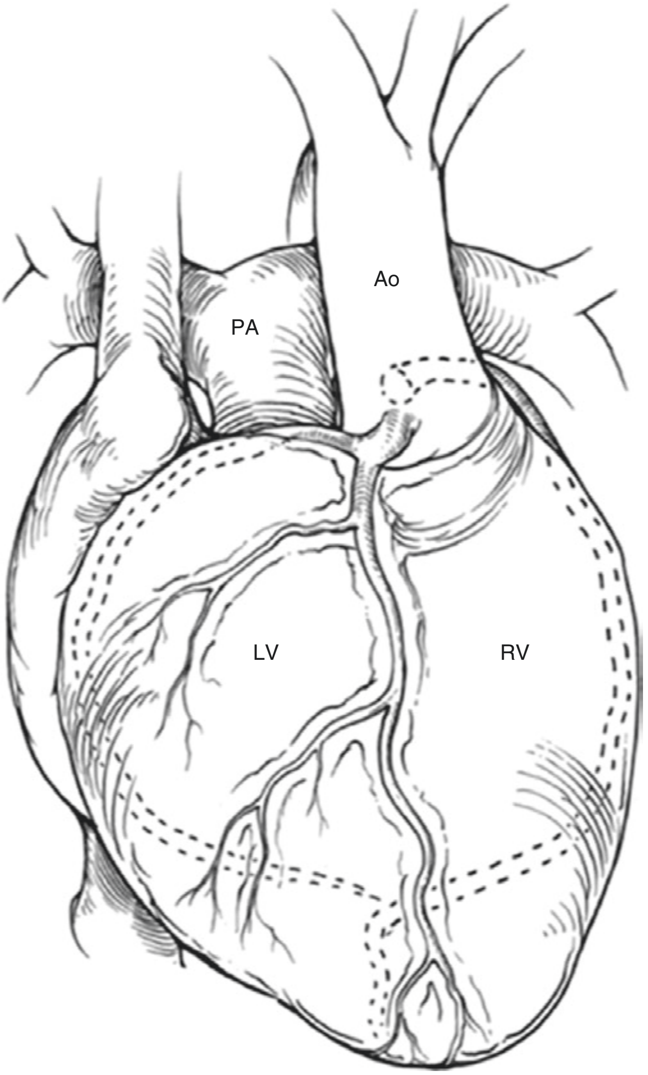


Fig. 100.1 External topography of congenitally corrected transposition of great arteries (ccTGA). There is atrioventricular and ventriculo arterial discordance. The aorta is anterior and to the left of the pulmonary artery (l-malposition). The morphologic right ventricle is leftward (l-loop)

close to the commissure between anterior and posterior mitral valve leaflets. This accessory AV node gives rise to a long penetrating His bundle which runs through the fibrous trigone and passes subendocardially anterior and caudal to the pulmonary valve annulus. It continues as the left bundle on the morphologic left side of the septum while the right bundle penetrates the septum to fan out on the right morphologic side of the septum. In the presence of VSD the His bundle runs in close contact with the pulmonary valve annulus and proceeds to the anatomic left side anterior and superior rim of the VSD (Fig. 100.2). In few cases with dextrocardia there are anterior and posterior AV nodes with

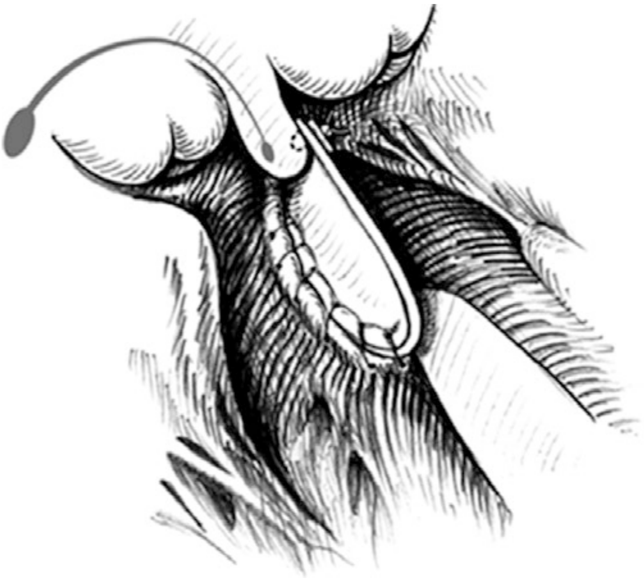


Fig. 100.2 Conduction system. The atrioventricular node (AV) node is anterior. The His bundle passes anterior and caudad to pulmonary valve and the suspension vein of ventricular septal defect (conversed partially with patch)

His bundle arising from one or both. In situs inversus the posterior node is normally located, and the penetrating bundle is located at the inferior and posterior rim of the VSD similar to hearts with atrioventricular concordance. The long and abnormal course of the His bundle predisposes it to continued mechanical stress and could result in spontaneous complete AV block at a rate of 2% per patient year [10, 11].

Pathophysiology and Clinical Presentation

The clinical presentation of patients with ccTGA is varied, because of the diversity of associated defects. In the absence of other malformations, patients with ccTGA are asymptomatic early in life. However, progressive deterioration of the systemic morphologic right ventricle could occur with age. Symptoms of heart failure might develop when the patient reaches the forth decade of life. Concomitant tricuspid valve regurgitation due to annular dilation caused by a dilated ventricle and the onset of spontaneous complete AV block could accelerate the onset of symptoms [12–15].

When associated lesions are present, the clinical course is dictated by these lesions [12]. An isolated large VSD results in progressive congestive heart failure early in life when the pulmonary vascular resistance starts to drop. Late onset of progressive, irreversible pulmonary vascular disease occurs later if the condition is not treated surgically.

Isolated pulmonary stenosis results in morphologic left ventricular hypertension, which if not severe, is well tolerated. Severe pulmonary stenosis or atresia presents with hypoxemia and requires early surgical intervention.

When pulmonary stenosis is present with VSD, circulation is usually balanced, and oxygen saturation is adequate. Most of those patients do not need palliative procedure or complete repair early in life. As pulmonary blood flow decreases with time due to progressive obstruction of morphologic left ventricular outflow, the resultant increase in the degree of desaturation necessitates palliative shunt or definitive intervention.

Isolated tricuspid insufficiency due to valve abnormalities varies in severity. Progressive dilatation of the morphologic right ventricle and shifting of the septum towards the left ventricle due to decrease in its cavitary pressure adds to the severity of the regurgitation and necessitates medical and/or surgical treatment.

Diagnosis

The chest X-ray in ccTGA has a characteristic straight left heart border due to the leftward and anterior position of the aorta (Fig. 100.3). The electrocardiogram may show conduction disturbances and a Q wave in right pericardial lead. Two-dimensional echocardiogram reveals apical displacement of tricuspid valve. The right ventricle is identified by the presence of the moderator band and the extensive trabuculation of its wall (Fig. 100.4). The atrioventricular and ventricular arterial discordance is quite evident. Cardiac catheterization is needed to evaluate the different hemodynamic parameters.

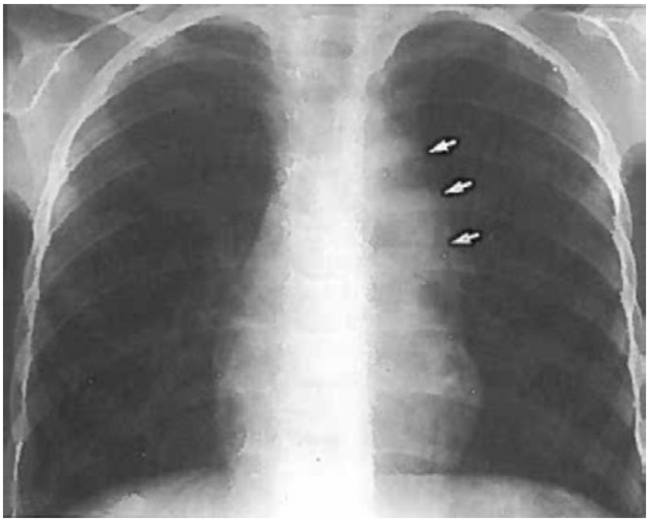


Fig. 100.3 Chest X-ray of patient with congenitally corrected transposition of great arteries (ccTGA). There is straight left heart boarder due to l-transposition of the aorta

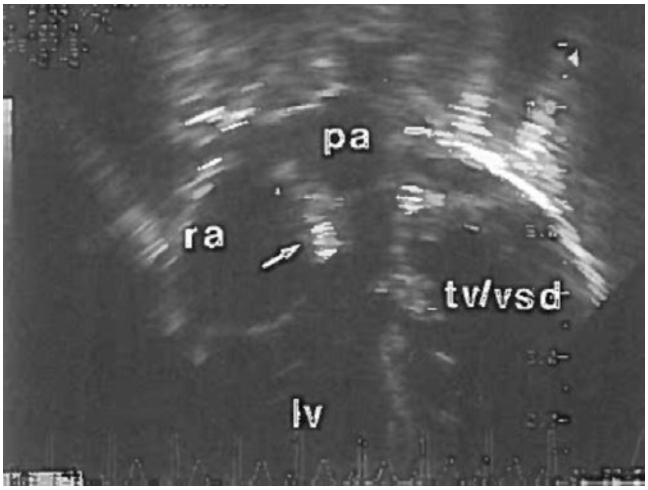


Fig. 100.4 Echocardiographic image of congenitally corrected transposition of great arteries (ccTGA). The pulmonary artery arises from morphologic left ventricle. The right ventricle is identified by the tricuspid valve and the moderator band

Surgical Treatment

The surgical approach to patients with ccTGA depends on the presence and severity of the associated lesions.

ccTGA with Isolated Left Ventricular Outflow Tract Obstruction

It is unusual for this combination to cause any significant symptoms. Although the morphologic left ventricle is hypertensive (close to systemic pressure in some cases), it can readily handle the increased afterload by virtue of its morphology and function. As a result, treatment might not be needed until the patient is older. There is also an added benefit of leaving a moderately hypertensive left ventricle. It minimizes the interventricular septal shift away from the dilated right ventricle. Consequently, it reduces ventricular wall tension and tricuspid valve annular dilation. Several procedures have been used to relieve the left ventricular outflow tract (LVOT) obstruction. These include resection of the subvalvar obstructive tissue with or without pulmonary valvotomy. Although helpful in reducing the left ventricular pressure, this approach carries a high incidence of post-operative complete AV block, and has been generally abandoned. Placement of a valved conduit between the left ventricle and main pulmonary artery relieves the LVOT obstruction, but necessitates repeated surgeries for conduit replacement (Fig. 100.5). Addition of a pulsatile bidirectional Glenn shunt reduces the volume load on the left ventricle and the conduit thereby potentially decreasing the LVOT gradient and prolonging conduit functional life (Fig. 100.6) [16].

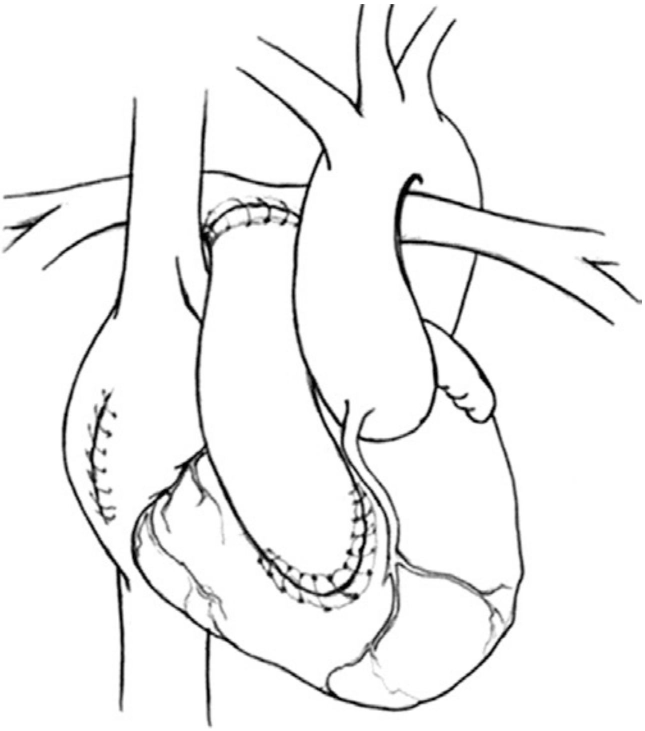


Fig. 100.5 The “physiologic” repair of patients with left ventricular outflow obstruction. A valved conduit is placed between the morphologic left ventricle (pulmonary ventricle) and the pulmonary artery

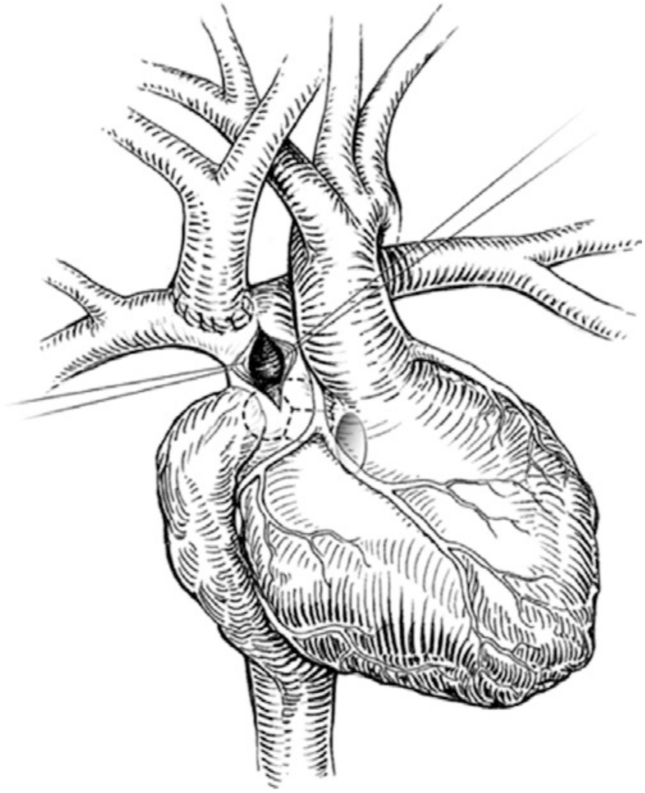


Fig. 100.6 A pulsatile Glenn shunt is used to bypass the obstructed left ventricular outflow tract. Additional valvuloplasty is performed through the pulmonary artery

ccTGA with Pulmonary Stenosis/Atresia and Ventricular Septal Defect

Until late 1980s, the surgical treatment of this combination of lesions was directed towards a physiologic repair leaving the right ventricle as the systemic ventricle. The VSD was closed through the mitral valve and the obstructed LVOT was bypassed by a left ventricle to pulmonary artery (LV-PA) valved conduit. Follow up of patients thus treated revealed several drawbacks to this repair [17]. The closure of VSD had a high incidence of postoperative complete AV block in spite of placing the sutures on the morphologic right side of the septum through the VSD (Fig. 100.7). The LV-PA conduit had a shortened functional life and required repeated interventions. Most importantly however, there was progressive deterioration of right ventricle and tricuspid valve functions leading to severe heart failure, transplantation or death. Due to these disappointing results, the concept of anatomic correction or the double switch operation (the Ilbawi Procedure) was introduced [18, 19]. It consists of an arterial and venous switch procedures. Through a right ventriculotomy, the VSD is tunneled into the aorta using a large synthetic patch fixed in place with interrupted and continuous sutures (Fig. 100.8). This morphologic right septal approach avoids the conduction system and practically eliminates postoperative AV block. This tunneling also directs the blood from the left ventricle into the systemic circulation thus establishing the left ventricle as the systemic ventricle.

A venous switch operation is performed to direct the pulmonary venous return to the morphologic mitral valve/left ventricle and the systemic venous return to the tricuspid valve/right ventricle (Fig. 100.9). A bidirectional Glenn procedure could be added to the venous switch operation (the so called hemi-Mustard) [20, 21] (Fig. 100.10). Finally, the pulmonary artery is transected. Its proximal end is over sewn and a right ventricle to pulmonary artery (RV-PA) valved conduit is placed.

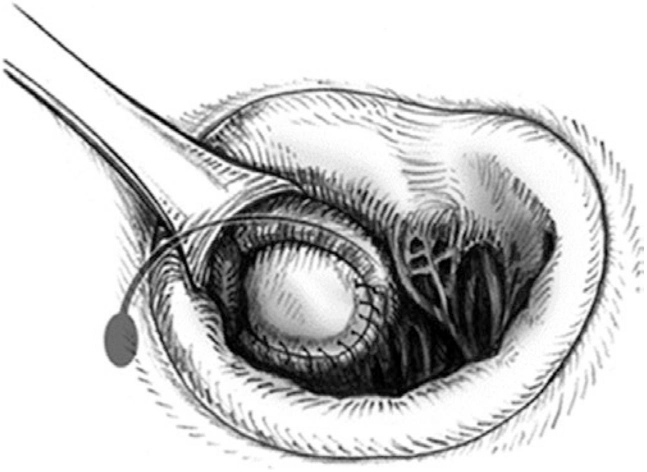
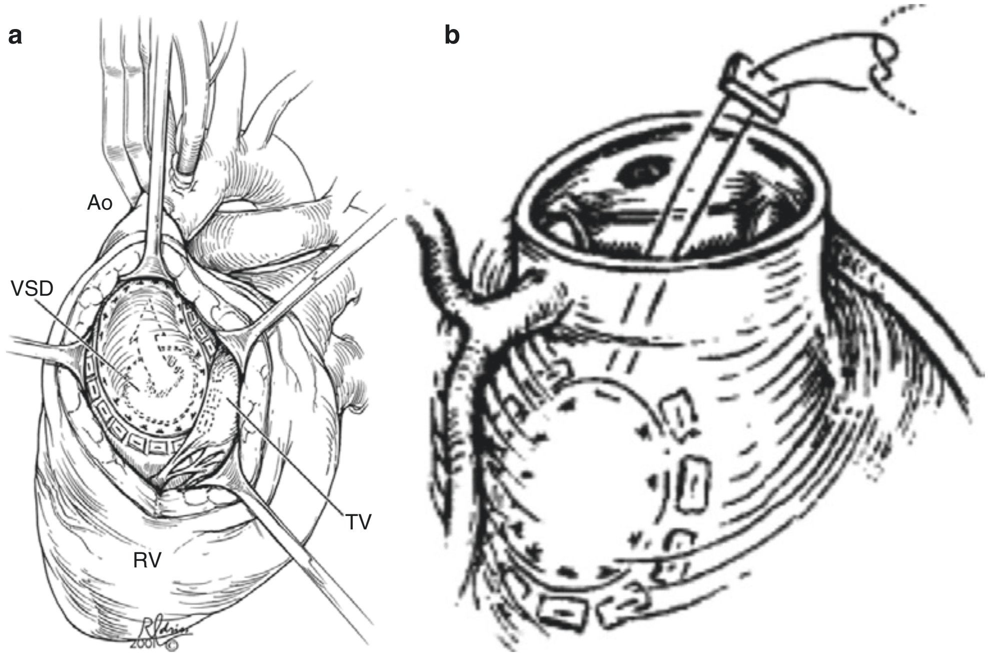


Fig. 100.7 Modified technique for closure of the ventricular septal defect. The sutures are placed on the morphologic right side of the septum superiorly and anteriorly to avoid the conduction system

Fig. 100.8 (**a**) Closure of the ventricular septal defect (VSD) through a right ventriculotomy. Sutures are placed on the morphologic right side of the septum and around the aortic root to tunnel left ventricular blood flow into the aorta (Ao) through the VSD. The defect can be enlarged inferiorly if judged to be restrictive. (**b**) Closure of the VSD through the aortic root in cases ventriculotomy is not needed



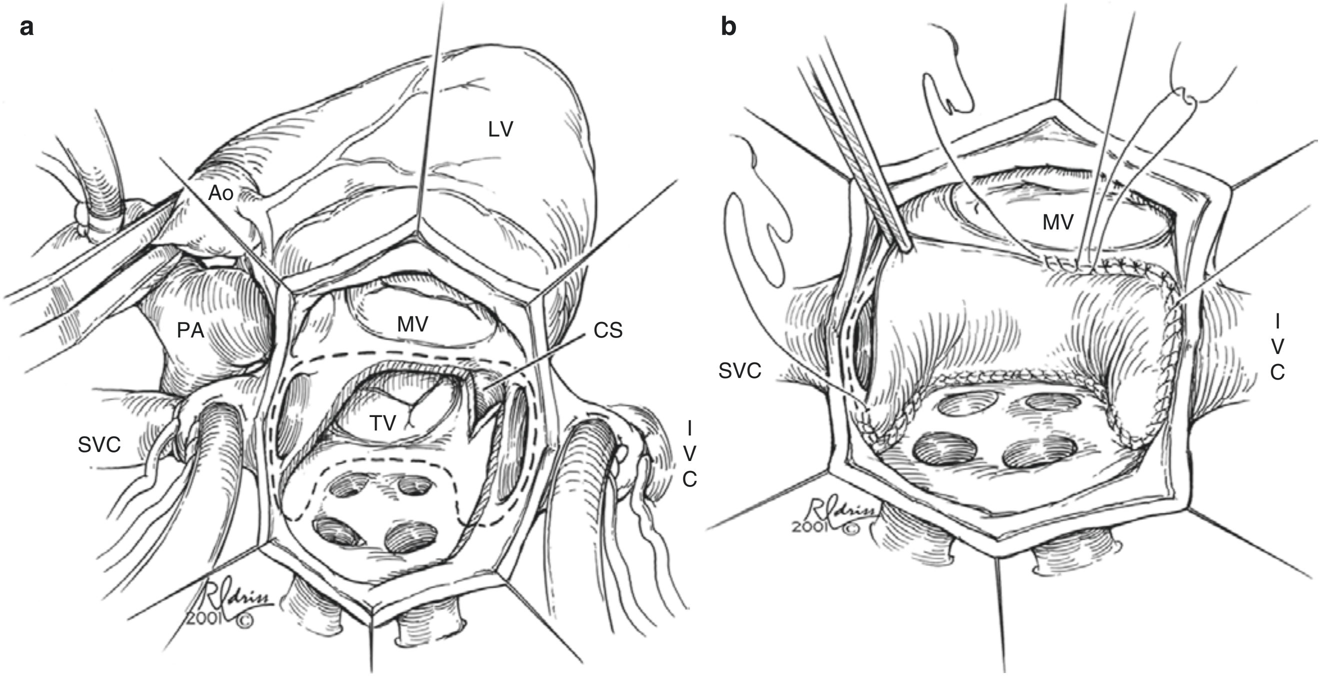


Fig. 100.9 Venous switch operation—Mustard procedure: (**a**) Total atrial septectomy is performed. The coronary sinus (CS) is unroofed towards the left atrium. The dotted line outlines the location of the intra atrial tunnel. (**b**) The constructed tunnel using untreated autologous pericardium. Interrupted sutures are used to secure pericardial patch to the floor of the unroofed CS. *Ao* aorta, *IVC* inferior vena cava, *LV* left ventricle, *MV* mitral valve, *PA* pulmonary artery, *SVC* superior vena cava

ccTGA with Tricuspid Valvar Insufficiency

Onset of tricuspid regurgitation is an ominous sign and mandates the need for early treatment. Tricuspid valvuloplasty in the form of enlarging the leaflets with autologous glutaraldehyde-treated pericardial patch combined with annuloplasty have been used. Valve repair in general has not been successful in this setting because of the very unusual pathology. However, it could be used with pulmonary artery banding as a temporizing measure to prepare the patient eventually for the double switch/anatomic repair and is probably the only good option for treating this subset of patients.

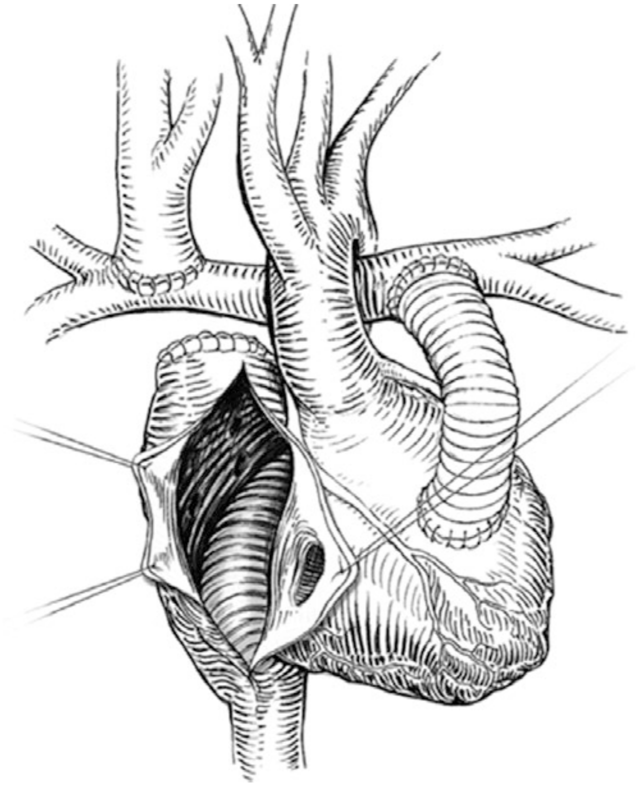


Fig. 100.10 The hemi-Mustard modification. The inferior vena cava is tunneled to the left atrium/tricuspid valve. A pulsatile Glenn procedure is used to direct the superior vena cava blood to the pulmonary circulation

The band might also help in preventing excessive shift of the septum towards the morphologic left ventricle, hence stabilizing the annuloplasty. Tricuspid valve replacement might be needed if regurgitation is severe. However, long-term results are not encouraging due to progressive right ventricular failure [17].

ccTGA with Isolated Ventricular Septal Defect

These patients are best treated with double switch operation and closure of VSD. The timing of the procedure is controversial. It could be performed in early infancy at the onset of symptoms or delayed by performing early pulmonary artery banding until the patient is around 6 months of age. This staged approach allows for growth of different structures, decreases pulmonary vascular resistance, and minimizes the risk of venous switch complications, while keeping left ventricle prepared for systemic pressure. Banding of the pulmonary artery, however, can potentially harm the neoaortic valve. The band, therefore, should be placed distally on the main pulmonary artery and the double switch operation preferably performed around 6 months of age, before onset of pulmonary root dilatation.

VSD is closed through the mitral valve with the sutures placed on the morphologic right side of the septum. It could also be closed through aortic valve (Fig. 100.11).

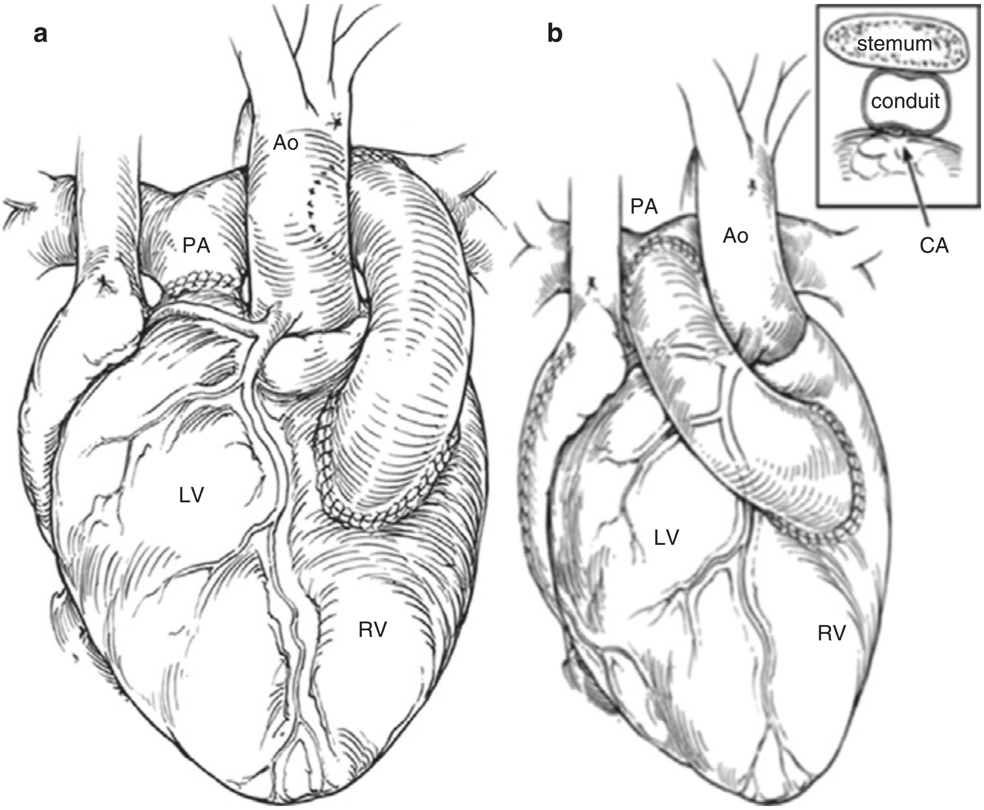


Fig. 100.11 (**a**) The right ventricle (RV) to pulmonary artery (PA) conduit is placed to the left of the aorta (Ao) after appropriate beveling. (**b**) The conduit is placed to the right side of aorta. In this location, there is potential risk of compression of the conduit by the sternum, and the right coronary artery (CA) by the conduit

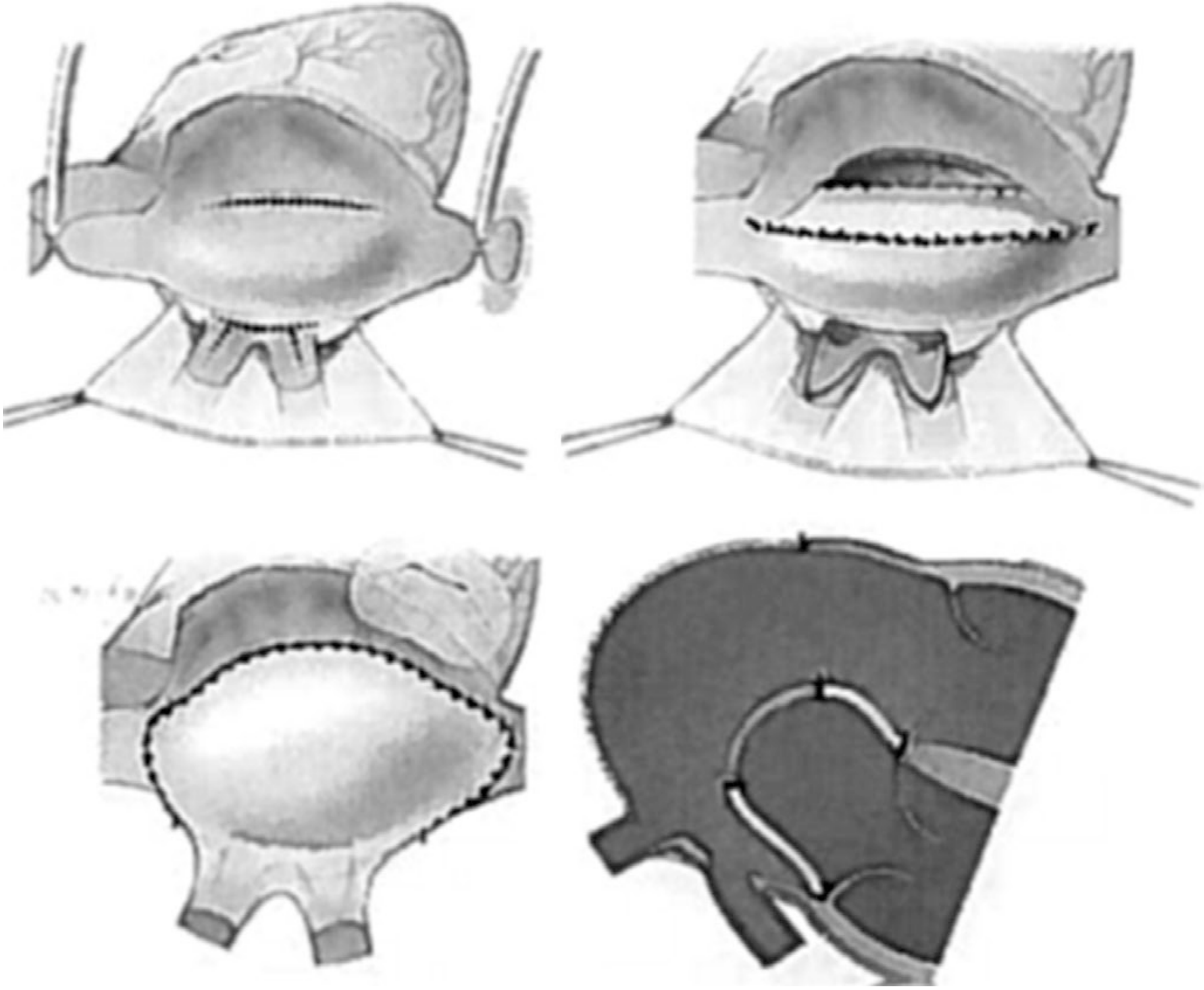


Fig. 100.12 Venous switch technique using the Senning technique. Dotted lines outline the incisions into the right and left atria. The detached septum is enlarged by patch material and sutured to the rim of the left sided valve. The external wall of the "functional" left atrium is then reconstructed with another patch

The venous switch operation is performed using the Mustard or Senning procedure (Figs. 100.9 and 100.12). The Mustard procedure has several advantages [22]. It is more versatile, and the suture line is easily modified to fit the space. It can be performed in patients with isolated dextrocardia where the right atrium is small and posterior. It has lower incidence of sinus node dysfunction and venous pathway obstruction. It can be performed in conjunction with bidirectional Glenn, the so-called hemi-Mustard procedure, which simplifies the technique and minimizes the complications of the venous switch (Fig. 100.13).

The arterial switch is performed in the usual fashion as previously described. Thorough mobilization of the coronary arteries and the use of a trap door technique have been especially helpful in ccTGA due to the orientation of the great vessels (Fig. 100.14). LeCompte maneuver may not be needed [23].

Alternative Procedures

When biventricular repair is not possible due to straddling AV valve, ventricular hypoplasia or distant muscular VSD, single ventricle palliation is an attractive alternative approach. It provides good midterm results in this subgroup where the left ventricle remains the main systemic ventricle.

Aortic translocation is another good alternative in patients with LVOT obstruction and distant ventricular septal defect. In this procedure the aortic root with the coronary arteries is detached from the underlying right ventricle and translocated into a longitudinally opened LVOT (Fig. 100.15). Ventricular septal defect is closed with a patch and RV-PA continuity is established usually without the use of a conduit.

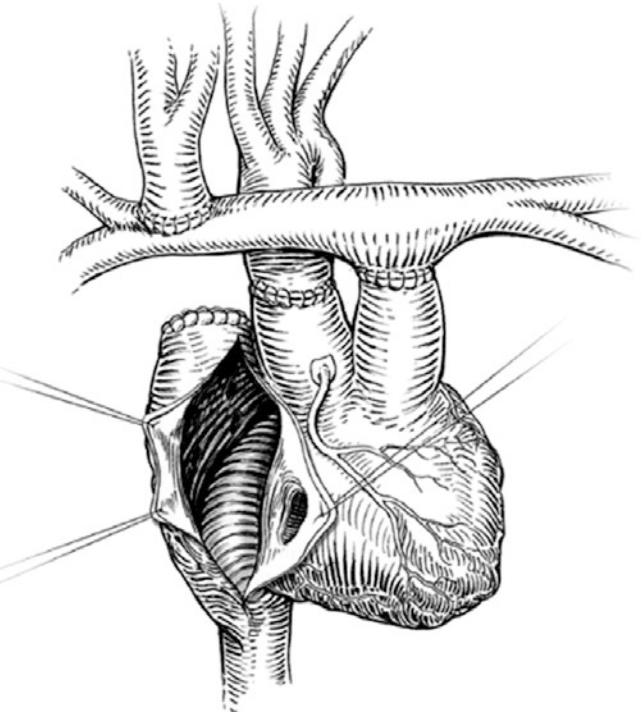


Fig. 100.13 Arterial switch operation performed in conjunction with hemi-Mustard procedure

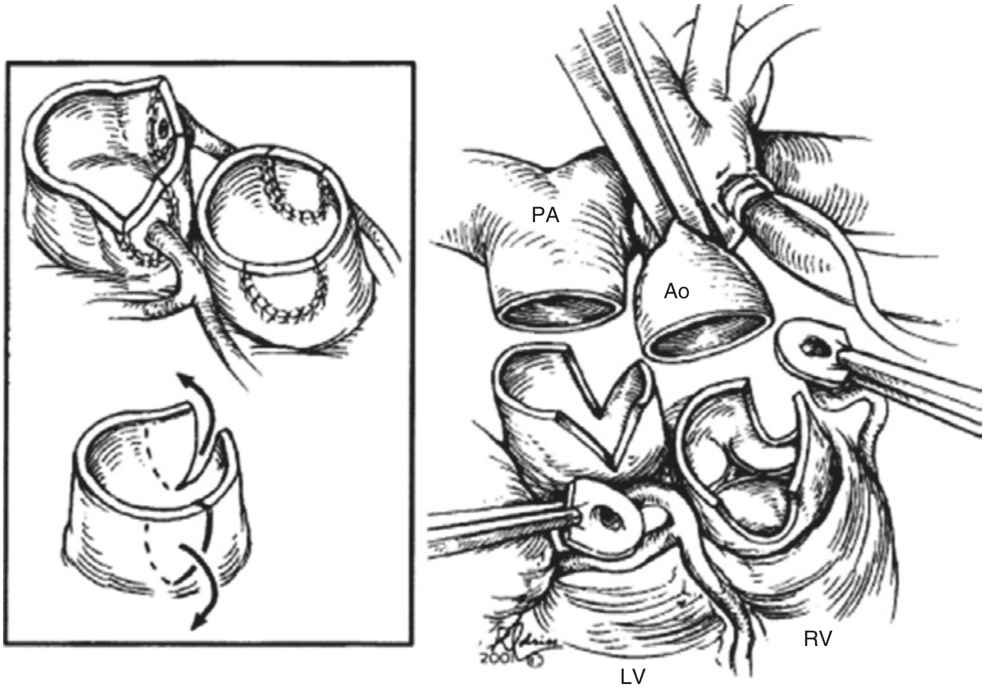


Fig. 100.14 Details of the arterial switch operation. Trap doors into the neoaortic root are helpful to minimize distortion. Extensive mobilization of the coronary arteries is helpful

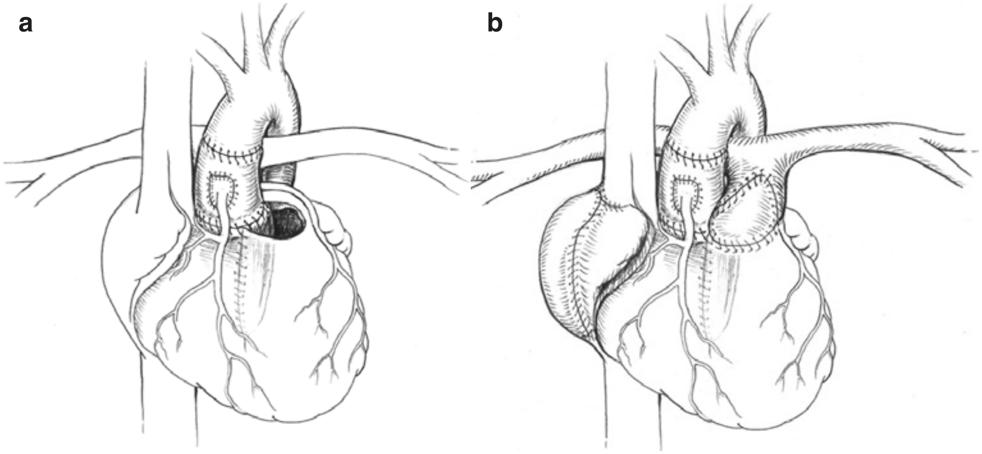


Fig. 100.15 (**a**) Aortic translocation for ccTGA with ventricular septal defect (VSD) and pulmonary stenosis. The aortic cannula is placed very cephalad. Aortic root is mobilized circumferentially. A wide rim of right ventricular (RV) free wall is left attached to aortic root. Extensive coronary artery mobilization is performed. The main pulmonary artery is transected proximal to bifurcation. A longitudinal incision into the left ventricular outflow tract (LVOT) is performed. The aortic root is sutured to the LVOT posteriorly and to a VSD patch anteriorly. Coronary arteries are either left attached to the aorta if there is no kinking or detached and reimplanted on the neonate. (**b**) The main pulmonary artery is connected to RV outflow tract and a patch is used to enlarge it

Results

Outcomes of the "physiologic" repair have been disappointing. Many reports have demonstrated progressive right ventricle failure in patients who have associated lesions. Survival was around 61.1% at 15 years postoperatively, and many patients needed transplantation. Patients with tricuspid regurgitation had the worst outcomes. These discouraging results of the physiologic repair prompted the adoption of anatomic repair as the treatment of choice. Excluding the learning curve results, short and long-term outcomes of anatomic repair have been excellent with operative mortality of 0–7%. Ventricular function is also preserved with near normal biventricular ejection fraction on follow up. Tricuspid regurgitation seems to improve, and perioperative complete AV block is rare [24–26].

Summary

Although the experience with double switch operation is limited to small series and varies with institutional experience, the results are generally very satisfactory, and the complications of venous switch operation have been minimal due to recent modifications. However, long term outcome is not available. It requires a longitudinal multi-institutional study to confirm that patients with ccTGA are best served by using the left ventricle as the systemic ventricle.

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Tetralogy of Fallot

101

Damien J. LaPar and Emile A. Bacha

High Yield Facts

- Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart disease beyond 1 week of age.
- TOF has an incidence of 0.19–0.26/1000 live births.
- TOF was originally described by Etienne-Louis Arthur Fallot.
- Characteristic morphologic features of "classic" TOF relate to aberrant conotruncal development, resulting in anterior malalignment of the infundibular septum relative to the conotruncus.
- Morphologic features of "classic" TOF include: (1) anterior malalignment ventricular septal defect, (2) over-riding aortic valve [relative to interventricular septum], (3) right ventricular outflow tract obstruction (RVOTO), and (4) right ventricular hypertrophy.
- RVOTO may occur with any combination of obstruction to antegrade pulmonary blood flow at the subvalvar (infundibular), valvar, or supravalvar (main or branch pulmonary artery) level.
- A pulmonary valve-sparing complete TOF repair technique has become popularized in the modern surgical era (vs. the classic repair with transannular patch).

Introduction

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart disease beyond 1 week of age. It has an incidence of 0.19–0.26/1000 live births. Neonates are often asymptomatic. The right ventricular outflow tract (RVOT) stenosis tends to increase with time, and infants typically become symptomatic after a few months of age [1, 2]. The purpose of this chapter will be to review the morphologic and physiologic features of "classic" TOF with an emphasis on contemporary approaches to surgical treatment.

Anatomy and Morphology

TOF is a classic cyanotic congenital heart defect, originally described by Etienne-Louis Arthur Fallot. The characteristic morphologic features of "classic" TOF relate to aberrant conotruncal development, resulting in anterior malalignment of the infundibular septum relative to the conotruncus. As a result, patients develop a large (usually nonrestrictive) anterior malalignment, subaortic ventricular septal defect (VSD) with concomitant anteriorly displaced aortic valve that "over-rides" the VSD (relative to the interventricular septum) as well as varying degrees of right ventricular outflow tract obstruction (RVOTO) and secondary right ventricular hypertrophy.

There are several commonly associated lesions with TOF. The most common concomitant conditions associated with TOF include, persistent left superior vena cava (LSVC), presence of additional muscular VSDs, presence of patent foramen ovale (PFO) or small secundum atrial septal defect, persistence of a small patent ductus arteriosus with normal ductal insertion, a right aortic arch (~25%), and anomalous coronary arteries (~5%). The most common coronary anomaly associated with TOF is an anomalous origin of the anterior descending coronary artery from the proximal right coronary artery (RCA) with

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a course that crosses the distal right ventricular outflow tract in the area of the subpulmonary infundibulum. A much less frequent anomalous RCA originating from the left main coronary artery trunk that crosses the subpulmonary infundibulum can also occur. The presence of anomalous coronary arteries have significant implications on the surgical approach to management of the RVOT at the time of repair.

TOF has also been associated with various chromosomal abnormalities. An association with chromosome 22q11.2 deletion and in some DiGeorge syndrome occurs in ~15% of TOF patients. Trisomy 21 and Downs syndrome occurs in 5–10% of TOF patients. Other genetic disorders, including Alagille syndrome and CHARGE syndrome, have also been rarely described in TOF patients.

Pathophysiology

TOF is by definition a cyanotic congenital heart defect that may present with varying degrees of RVOTO and cyanosis. The RVOTO may occur with any combination of obstruction to antegrade pulmonary blood flow at the subvalvar (infundibular), valvar, or supravalvar (main or branch pulmonary artery) level. Most commonly, multi-level RVOTO is present in symptomatic, cyanotic patients. The degree and extent of RVOTO usually dictates the underlying pathophysiology of this condition. For some neonates with severe multi-level RVOTO, the cyanosis may be severe enough such that the child has ductal dependent pulmonary blood flow. The majority of TOF patients, however, present with mild-to-moderate degrees of RVOTO and remain asymptomatic in the neonatal and early infant period of life. With growth and progressive hypertrophy of the right ventricle and infundibulum, the patient develops increasing right ventricular pressures resulting in the development of a right-to-left shunt through the VSD, resulting in progressively increasing cyanosis and propensity for profound desaturation (i.e. hypercyanotic) events. The most severe hypercyanotic episodes, "Tetralogy spells," are characterized by the constellation of hypercyanosis, hypoxia, hyperpnea, and syncope with loss of consciousness. On the opposite end of the clinical spectrum, are patients with minimal to no RVOTO in the presence of a large, nonrestrictive, anterior malaligned VSD. These patients with "pink Tetralogy" often present with unobstructed antegrade pulmonary blood flow and normal oxygen saturations with left-to-right shunting though the VSD. Contrary to patients with TOF/pulmonary stenosis, these patients present with signs and symptoms of pulmonary overcirculation and congestive heart failure as the pulmonary vascular resistance decreases with age.

Approach to Surgical Decision Making in the Modern Surgical Era: Pulmonary Valve Preservation and the Scope of the Problem

Initial approaches to TOF repair in the 1960s and 1970s mostly commonly employed the use of large transannular RVOT patches [3]. As a result, chronic RV volume loading due to free pulmonary regurgitation (PR) after transannular patch placement is now recognized as deleterious to the RV [3]. Moreover, late sequelae from chronic PR after TOF repair with a transannular patch include RV dilation, RV diastolic dysfunction, RV fibrosis, tricuspid regurgitation (annular dilation, but sometimes due to surgical changes at the site of the VSD patch), arrhythmias (risk of ventricular arrhythmias) [4], and, in late stages, left ventricular (LV) dysfunction. In addition, the RVOT patch itself can act as an energy sink especially when large and patulous [5].

In the contemporary surgical era, most surgeons agree that pulmonary valve preservation during TOF repair is beneficial. The clinical dilemma, however, centers on how to negotiate the two extremes of pulmonary stenosis (PS) and PR? In an ideal surgical scenario, a complete TOF repair would result in no regurgitation and no residual RVOT stenosis. Since this is rarely possible, the surgeon is often left with determining how much residual PS or PR is acceptable to leave after primary repair.

A recent survey of the Society of Thoracic Surgeons (STS) Database concluded by stating that "despite contemporary awareness of the late consequences of pulmonary insufficiency, ventriculotomy with transannular patch remains the most prevalent technique, both for primary repair and for repair following palliation" [1].

Surgical Management

Our departmental approach to the surgical repair of TOF at the New York-Presbyterian/Morgan Stanley Children's Hospital at Columbia University and Weil-Cornell University is that any symptomatic TOF patient is considered for complete, primary repair, provided the anatomy is well characterized and suitable. In our practice, the role for palliative aorto-pulmonary shunts (e.g. modified Blalock-Taussig shunt) in TOF/PS has become limited to a very small subset of patients, such as those with anomalous left anterior descending artery crossing the RVOT, or with significant non-cardiac problems. In our experience, shunts have nearly as much morbidity associated with them as primary repair. As a result, symptomatic neonates with TOF and suitable anatomy typically undergo complete, primary repair. However, the majority of TOF patients typically undergo elective repair between 3 and 9 months of age.

Standard cardiopulmonary bypass techniques with bicaval cannulation and moderate hypothermia are usually employed. Intraoperative transesophageal echocardiography (TEE) is performed in every case to assess the anatomy, and later adequacy of the repair. We believe it is crucial that the surgeon and imaging cardiologist collectively study the TEE findings preoperatively to develop a good understanding of the relationship between imaging features and intraoperative findings.

After complete dissection and control of the branch PAs, a marking suture is placed at the precise midpoint of the distal main pulmonary artery (MPA) to guide the future direction and distal extent of the MPA incision to avoid skiving into or toward the left (LPA) or right (RPA) pulmonary artery. Using cardioplegic cardiac arrest, the right atrium is opened and the intracardiac anatomy is inspected. If no PFO is present, we create a small atrial septal opening through which we place an LV vent. The VSD is inspected and a decision is made to close the VSD transatrially or transventricularly. In virtually every case the MPA is opened longitudinally with the proximal extent carried down to the pulmonary valve annulus in order to adequately inspect and assess the pulmonary valve. We have a low threshold to open the RVOT through an infundibulotomy, keeping the incision length as minimal as possible and limited to the infundibulum. While we recognize that some surgeons are reluctant to make an incision in the RVOT, preferring to always close the VSD and divide obstructing muscle bundles though the tricuspid valve and through the pulmonary valve (transatrial approach), in our experience we have not encountered sufficient long-term evidence to support one technique over another (i.e. transventricular vs. transatrial).

VSD Closure and RVOT Muscle Bundle Resection

Extensive RVOT muscle bundle resection is then performed paying particular attention to the septal band and parietal bands as well as the trabecula septomarginalis which should be preserved to serve as anchoring site for VSD sutures. The VSD is closed either with interrupted or with continuous suture technique. Generally, we favor an interrupted approach (usually through the RVOT), using 5-0 Tevdek sutures with pledgets. Various patch materials including autologous pericardium, preserved xenopericardium, and various prosthetic materials (e.g. polyethylene terepthalate [Dacron, DuPont, Wilmington, Del], polytetrafluoroethylene [Gore-Tex, W. L. Gore & Associates, Inc., Flagstaff, Arizona], or CorMatrix [Aziyo Biologics, Silver Springs, MD, USA]) may be utilized. Regardless of technique, careful attention to placing the sutures adjacent to the aortic valve annulus will help to avoid the presence of residual intramural VSDs.

Approach to the Pulmonary Valve

The pulmonary valve is then inspected for size and morphology. The surgeon should be aware of the normalized size of the pulmonary annulus for the patient's body surface area (BSA). Typically, we aim to achieve at least 2 mm less than the ideal orifice size. Based on the diameter of the pulmonary annulus and the anatomy of the cusps, a decision is made whether to preserve the annulus or perform a transannular patch (z score of −2 is sometimes used as cut-off). One has to keep in mind that z scores are normalized values that are based on annular diameter measured by echo, which is not the same as the effective valve orifice. For example, one can have (albeit rarely) a small z score (i.e. large annulus) but a very dysplastic valve resulting in small effective orifice.

Surgical Options for Valve-Sparing TOF Repair

We believe that in all cases of TOF repair, the following surgical tenants should be observed:

- Complete infundibular muscle resection: including the area just under the annulus (either via limited infundibulotomy or via transatrial/transpulmonary)
- Pulmonary valve commissurotomy: into the media layer and down into the commissural triangle, usually using a #15 scalpel blade
- MPA longitudinal incision and patch augmentation: occasionally including the posterior sinuses as well (either patch or just incision)
- Residual small PFO: to provide decompression of the right side of the heart in the initial perioperative period during RV recovery/remodeling.

Mild-Moderate Pulmonary Stenosis and Mildly Dysplastic Valve

The simplest technique is commissurotomy alone and the release of any subvalvar muscle bands or fibrous attachments. A Hegar dilator can be used to measure the orifice before and after and also to gently dilate the pulmonary valve under direct vision.

Moderate Pulmonary Valve Stenosis or Dysplasia

Commissurotomy and Intraoperative Balloon Pulmonary Valve Dilation

Experience from percutaneous transcatheter balloon dilation of isolated pulmonary valve stenosis suggests that valve annuli grow over time. As opposed to Hegar dilation, a balloon

(Boston Scientific®, Mustang Balloon dilation catheter) can be introduced in a valve annulus at a diameter much smaller than the orifice, and dilation occurs in static position. The advantage of balloon dilation is the progressive radial transmission of stress throughout the entire valve annulus, which is lost with simple dilation using a Hegar dilator. Radial annulus dilation potentially allows for remodeling and growth of the pulmonary annulus.

The surgical technique for this approach is well described. Following commissurotomy, the effective valve orifice is sized with a Hegar dilator. Starting with a balloon 1 mm larger than the Hegar size that passes easily through the pulmonary valve, the balloon is passed either via the infundibular incision (New York/Boston technique) or via the unopened RVOT transatrially (Padua technique) and inflated by hand. Hand inflation (usually 10 cc syringe) is important as the inflation is monitored visually. The stretching of the cusps and annulus fibers can be observed and appreciated in real-time, and the inflation stopped if a tear starts to occur. The balloons are gradually increased in size by 1 mm increments. One can often see the very beginning of a tear at the free edge of the anterior cusp, indicating the cessation of balloon inflation. Both the PA incision and the RVOT incision are then patched, paying particular attention to the distal RVOT patch which has to be rounded and sutured carefully to avoid narrowing of the enlarged subannular area. Interrupted suture technique is often used in this area.

In an initial series of 32 patients with z scores between −2 and −4 who received intraoperative balloon pulmonary valve dilation, evidence for annular growth over time was seen, with normalization of the pulmonary annular size in many patients [6]. As compared with a similar group which received transannular patches, a higher reintervention rate was seen due to residual PS (mostly managed via transcatheter balloon dilation) in the intraoperative balloon pulmonary valve dilation group. A subset of patients where this technique is useful is those with anomalous coronary crossing the RVOT.

Valve-Sparing Transannular Reconstruction

For patients who would otherwise require a transannular patch, a valve-sparing transannular reconstruction technique (Fig. 101.1) can be utilized whereby the valve is split and reconstructed [7–9]. If the valve commissures are oriented in a coronal plane (i.e. one left and one right commissure), then the annulus and anterior cusp are divided in the midline as for a transannular patch, leaving equal cusp remnants on each side. The tethering of the anterior cusp to the MPA is left to preserve hinge function of a newly created large anterior cusp. If the valve is oriented in a sagittal plane, then the incision goes through the anterior commissure. This is a less favorable situation. Native pericardium can be used as patch material, but also 0.1 mm PTFE (Goretex) or extracellular matrix (Cormatrix). The width of the patch is tailored according to the fraction of the Hegar dilator circumference exposed at the annulus during RVOT calibration. The patch is sutured to each cut cusp edge, leaving 1–2 mm of patch protruding distally over the free edge of the valve. Caudally, the suture line continues along the endocardial edge of the RVOT incision, leaving the epicardial edge free to receive the second "roofing" patch. Once done, a second (transannular) patch is sutured over the entire length of the PA and RVOT incision as a "roof".

Regardless of RVOT technique, the operation is completed by leaving a small atrial communication, testing the tricuspid valve for function and competency, closure of the

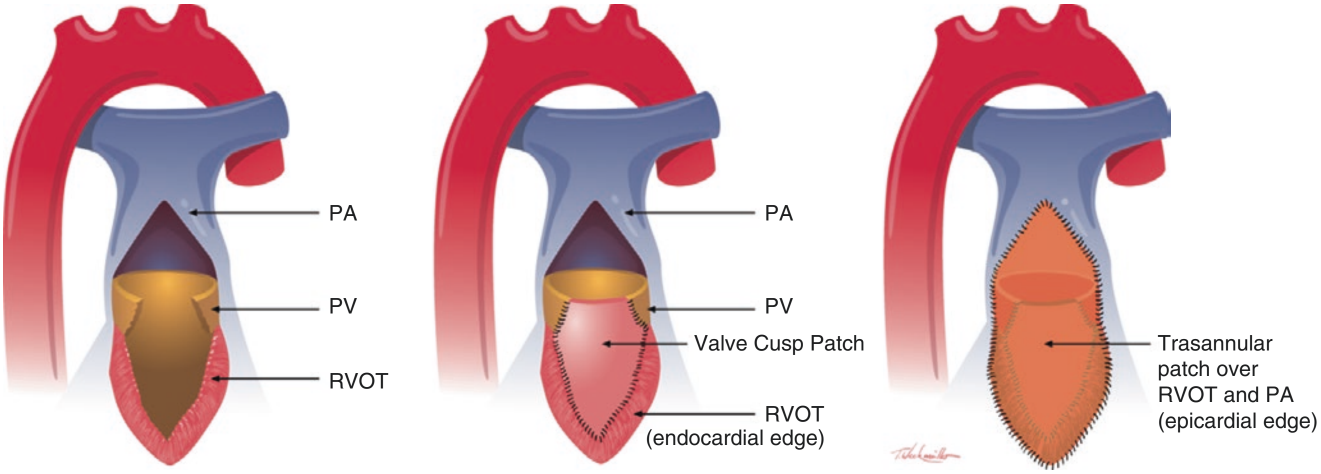


Fig. 101.1 Valve-sparing transannular reconstruction (VSTAR). A longitudinal incision is made from the distal pulmonary artery (PA) to the right ventricular outflow tract (RVOT). The anterior valve cusps are preserved and used to suture a patch from the valve to the end of the RVOT incision, securing the patch to the endocardial edge of the incision. A second patch is them sutured as a "roof" to cover the entire extent of the incision, secured to the epicardial edge of the RVOT proximally

right atriotomy, de-airing of the left side of the heart, weaning from cardiopulmonary bypass support, assessment for residual lesions (VSD or RVOTO), direct measurement of RV pressure. Our goal is to achieve the lowest possible RV pressure following TOF repair. For most repairs, an RV pressure of ≤50% systemic is considered acceptable.

Perioperative Management

While practice patterns may vary among institutions, inotropic and mechanical respiratory support is often required perioperatively. We prefer epinephrine as a primary inotrope. The post-operative course depends on the degree of RV dysfunction (usually temporary; 24–48 h) and the status of the RVOT with respect to pulmonary regurgitation or residual pulmonary stenosis. As previously mentioned, we prefer to leave a small atrial level communication (i.e. PFO) to support the RV in the perioperative setting. As a general philosophy, we will accept transient cyanosis via a right-to-left atrial level shunt in favor of adequate cardiac output and systemic perfusion as the RV recovers and its diastolic function improves following repair.

Postoperative Outcomes

The approach to TOF repair has a wide range of individual surgeon variability. Any associated pulmonary artery narrowing or significant RVOTO should be addressed during the same operation. Similarly, significant residual VSDs (>3 mm in size) with significant residual left-to-right shunts (Qp:Qs > 1.5 or pulmonary artery oxygen saturation >80%) should be addressed especially in the setting of transannular patch repair with free pulmonary regurgitation. The combination of increased volume load from free PR and significant residual L-R VSD shunt with poor diastolic function of a hypertrophied RV can result in circulatory failure. The operative mortality for standard TOF surgery in the modern surgical era is low (~1–2%) [1]. Potential complications that may occur following TOF repair include RV dysfunction (usually transient), atrioventricular (AV) block (<3%), junctional ectopic tachycardia (JET, <5%), patch dehiscence with residual VSD (very poorly tolerated), and residual RVOT obstruction.

New York-Presbyterian Morgan Stanley Children's Hospital/Columbia University Outcomes

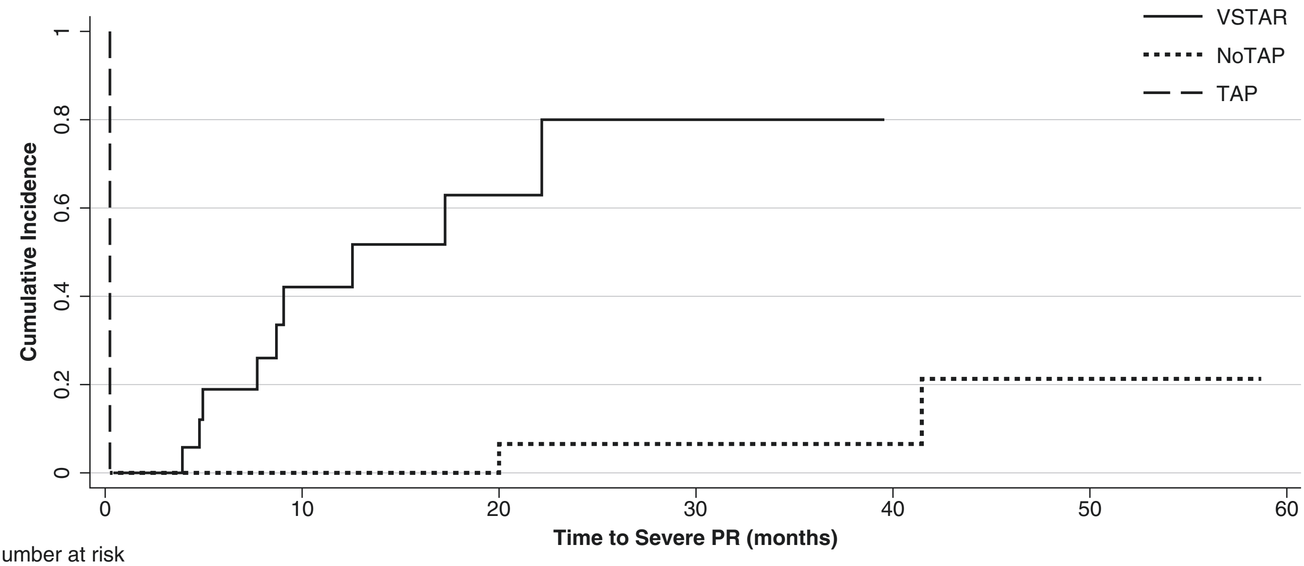
We adopted the aforementioned surgical strategy for complete TOF repair in 2010. In our experience, after excluding patients <6 weeks or age as well as all 'non-typical' TOFs (TOF/absent pulmonary valve, TOF/double outlet right ventricle, TOF with anomalous coronaries), 88 patients with "classic" TOF had pulmonary valve sparing approaches to repair between January 2010 and April 2016 [10]. The median age was 4 months. A valvotomy only was performed in 30%, valvotomy and balloon dilation in 32% and valve-sparing transannular reconstruction in 30%, while 8% received a transannular patch. There were no mortalities or major morbidities. During follow-up, three patients required a reoperation including two patients who had previous intraoperative balloon pulmonary valvotomy requiring a transannular patch and one patient who developed an RVOT aneurysm after valvotomy who also required repair of the aneurysm and transannular patch.

We observed an increase over time in PR (Fig. 101.2). At last follow-up, ~80% of valve-sparing transannular reconstruction patients had developed at least moderate PR by echocardiography. None however had required reoperation or developed pulmonary stenosis.

Conclusions and Perspective

In TOF surgery, the surgical implications of pulmonary valve anatomy have historically been neglected. During the past decade, increasing numbers of surgeons have focused upon pulmonary valve morphology and have attempted to push the boundaries in terms of valve preservation or valve reconstruction. An analysis of currently available literature is critical to not only understand the larger surgical experience of this approach to repair, but also to understand that z scores are simply normalized values of pulmonary annuli and do not reflect the degree of cusp dysplasia or effective orifice available. Thus, relying only on z scores can be misleading. We believe that z scores should continue to be evaluated as part of the overall surgical decision-making process. However, intraoperative inspection of the valve for direct repair technique is perhaps most important.

Congenital heart surgeons should start to think in terms of valve morphology and not only in terms of annular size. For mitral valves, Carpentier had popularized the "5-minute" rule, stating that surgeons should meticulously inspect the mitral valve for several minutes before attempting any repair. We believe in the same approach to the pulmonary valve in TOF repair. In summary, our experience with an aggressive philosophy of valve-sparing or valve-reconstructing TOF surgery has been positive. Continued refinements in technique are inevitable and long-term patient follow-up will provide further direction to optimize patient results.



Number at risk

VSTAR	19	11	7	3	8	2	0
NoTAP	29	19	15	10	0	0	0
TAP	32	0	0	0	0	0	0

Fig. 101.2 Long term cumulative incidence of severe pulmonary regurgitation (PR) following Tetralogy of Fallot repair stratified by right ventricular outflow tract repair technique (No transannular patch (TAP) vs. valve-sparing transannular repair (VSTAR) vs. TAP)

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Hypoplastic Left Heart Syndrome

102

David J. Barron

High Yield Facts
- Hypoplastic left heart syndrome (HLHS) is the single commonest cardiac cause of neonatal death.
- HLHS occurs 2 per 10,000 live births and comprises 1.4–3.8% of congenital heart disease.
- First stage of surgery is performed in the first few days of life and is termed Norwood operation.
- Norwood operation involves reconstruction of the aorta and main pulmonary artery into a single structure and provision of pulmonary blood flow with either a Blalock-Taussig shunt or small right ventricle to pulmonary artery conduit.
- Norwood operation remains highest risk of all neonatal cardiac surgery with 85–90% in-hospital survival currently.
- Controversy persists over the best technique.
- RV-PA conduit is most widely used and gives more stable haemodynamics.
- Alternative to Norwood is a hybrid procedure placing bilateral pulmonary artery bands and a ductal stent. This is less popular and is mainly reserved for high risk cases and avoidance of cardiopulmonary bypass.
- Stage II of treatment is bidirectional Glenn shunt at 5–6 months.
- Stage III is completion total cavo-pulmonary connection usually at 4–4.5 years.
- Three stage surgery completes the Fontan circulation.

Introduction

Hypoplastic left heart syndrome (HLHS) is characterised by variable degrees of underdevelopment of the left ventricle (LV) and the left heart structures such that they are unable to support the systemic circulation. The persistent foetal circulation allows the newborn to survive birth, but the condition is lethal without treatment, usually within the first few days of life. Although rare, occurring in 2 per 10,000 live births, it is the single commonest cardiac cause of neonatal death [1].

The condition is recognised world-wide without any particular geographical or racial variation, and is slightly commoner in males [2]. There is no single genetic defect that has been consistently identified, but several individual genetic abnormalities have been sporadically associated with HLHS [3]. About 5–12% of cases are associated with chromosomal anomalies, of which the commonest is Turner's syndrome. Despite the limited evidence for consistent genetic aetiology, there is a weak familial risk in that a mother who has had a previous child with HLHS has a 2–4% risk of recurrence.

Prior to the 1980s there was no treatment that could be offered for HLHS and the condition was viewed as being universally lethal—until William Norwood of the Children's Hospital of Philadelphia introduced the concept of using the right ventricle to support the systemic circulation. The 'Norwood procedure' as it has become known, has undergone many modifications and reflects the impact that HLHS surgery has had on the development of neonatal cardiac surgery over the past 30 years. In HLHS the left ventricle remains underdeveloped and so survival depends on a functionally single ventricular circulation based on a systemic right ventricle.

Morphology and Clinical Implications

As the name implies, this is not single morphologic feature, but rather involves the concept of smallness of the entire 'left heart' that includes the ventricle itself, the mitral and aortic

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Table 102.1 Morphology included within the spectrum of hypoplastic left heart conditions

Hypoplastic left heart syndrome (under development of all left heart structures)	30–35% Mitral stenosis with aortic stenosis (MS/AS) 35–40% Mitral atresia with aortic atresia (MA/AA) 20–25% Mitral stenosis with aortic atresia (MS/AA)
Unbalanced complete AVSD	Unbalanced defect such that the LV component is small Usually small left AV valve and small aorta with coarctation
Mitral atresia with VSD and DORV	These patients may not require a Norwood procedure PA band may be adequate if aorta of good size
Isomerism	Commoner in right isomerism than in left isomerism Both may have unbalanced AVSD morphology with small LV

AA aortic atresia, *AS* aortic stenosis, *AV* atrioventricular, *AVSD* atrioventricular septal defect, *DORV* double-outlet right ventricle, *LV* left ventricle, *MA* mitral atresia, *MS* mitral stenosis, *PA* pulmonary artery, *VSD* ventricular septal defect

valves, the left heart myocardium and endocardium and the ascending aorta and arch. There are a variety of conditions that fall within the spectrum of HLHS (Table 102.1). The common factor is that, by definition, the left heart is underdeveloped such that it is unable to support the systemic circulation. The morphological features can vary from almost complete obliteration of the LV with aortic and mitral atresia, to hearts where there is a small but well-formed LV with small mitral and aortic valves and a small cavity LV. The ascending aorta is usually small in HLHS, often with a 'matchstick' like appearance. The typical features of HLHS are shown in Fig. 102.1. The smallest ascending aortas are found in the presence of aortic atresia and aortic size of <2 mm carries an increased operative risk. The aortic arch is also usually hypoplastic and there is commonly a coarctation shelf. A combination of a patent mitral valve with aortic atresia can lead to very high pressures in the small LV cavity and the development of coronary sinusoids, which also carries increased risk. Any obstruction to the pulmonary venous return, most commonly due to a restrictive or intact atrial septum in the setting of mitral atresia, can lead to severe pulmonary congestion and, in severe cases, lymphangectasia of the lungs.

The right ventricle is usually morphologically normal, but abnormalities of the tricuspid valve can occur with clefts or dysplasia of the leaflets. HLHS within the spectrum of unbalanced atrioventricular septal defect (AVSD) is often associated with asymmetrical common AV-valves which are frequently incompetent. Antenatal diagnosis is increasingly common as the features are often well seen at a standard 20 week foetal scan.

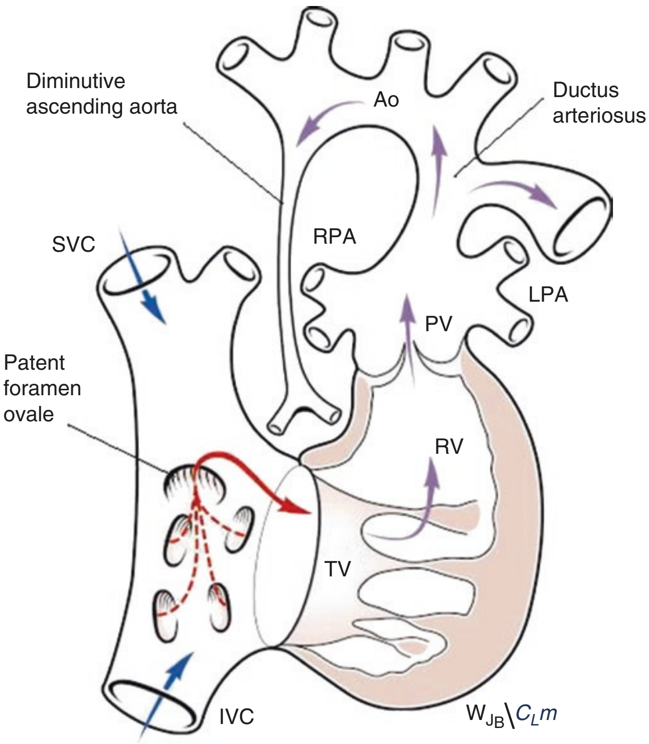

Fig. 102.1 Typical anatomy of Hypoplastic Left Heart Syndrome showing aortic atresia and a diminutive ascending aorta

Neonatal Management and the Norwood Operation

Survival depends on the ductus remaining patent and an adequate atrial communication. Since both these findings are common in the newborn, the babies may be born in good condition and only present when the duct begins to close with rapidly developing signs of cardiovascular collapse, tachypnoea and shock. Initial management is stabilisation with prostaglandin E2 infusion and supportive measures. Maintaining ductal patency may be all that is required, but shocked patients may require admission to intensive care unit (ICU), ventilation and stabilisation with inotropic support if necessary.

If the ductus remains open, patients will have uncontrolled pulmonary blood flow with a large volume load on the circulation and may develop signs of congestive heart failure with cardiomegaly, hepatomegaly, and pulmonary plethora with increasing tachypnoea. This may progress to respiratory distress, increasing acidosis and circulatory collapse. At the other end of the spectrum, patients with a restrictive foramen ovale or even intact atrial septum will have pulmonary venous congestion and be cyanosed and tachypnoeic from birth. Survival depends on the severity of the obstruction but severe cases will be profoundly cyanosed, rapidly decompensate and the situation will be incompatible with life.

Within this spectrum, cases may have a moderate sized duct and a degree of coarctation such that femoral pulses are weak or absent and there is evidence of congestive heart failure due to the combination of high pulmonary blood flow and high systemic after load. The degree of cyanosis is variable and although there is obligate mixing of the circulation, the high pulmonary blood flow may mask this, maintaining arterial saturations in the 90s.

Differential diagnosis includes neonates with other left-sided obstructive lesions which are duct dependent such as critical aortic stenosis, coarctation of the aorta and interrupted aortic arch. Other non-structural cardiac diseases, with clinical presentation in a shock-like state, such as neonatal myocarditis and neonatal sepsis can also mimic as HLHS.

Plain chest X-ray may reveal cardiomegaly with pulmonary plethora and oedema but is not diagnostic. An ECG is generally non-specific but may show signs of right ventricular hypertrophy with tall R-waves in the anterior leads. The heart rhythm is usually normal. The mainstay of diagnosis is by echocardiography, which can demonstrate all the aspects of the condition and confirm the diagnosis. Further imaging is rarely indicated and cardiac catheterisation normally has no role.

Norwood Operation

The condition is life threatening and definitive intervention is necessary as soon as the baby has been stabilised. The surgery is dependent on the fact that the neonatal right ventricle is able to function at systemic pressure since it has done so throughout fetal life. This allows it to be recruited to support the entire circulation.

Surgery has to achieve three things:

1. Ensure unobstructed venous return from the lungs into the circulation: this is achieved by performing an atrial septectomy—the floor of the fossa ovalis is excised such that the left and right atria are in free communication.
2. Ensure unobstructed outflow from the right ventricle to support the systemic circulation: this is achieved by joining the main pulmonary artery and the aorta together (Damus-Kaye-Stansel manoeuvre) and enlarging the small aortic arch and coarctation sites such that the right ventricle can eject freely into the unobstructed systemic circulation.
3. Achieve a balanced pulmonary blood flow: this is achieved by creating a shunt between the systemic and pulmonary circulations that provides adequate but not excessive pulmonary blood flow. This is achieved with either a Blalock-Taussig (BT) shunt or with a small right ventricle to pulmonary artery (RV-PA) conduit.

The Norwood procedure achieves these three fundamental principles (Fig. 102.2a, b). This is one of the most complex procedures in neonatal cardiac surgery and has undergone a variety of modifications over the past 30 years. It is ideally performed within 3–5 days of life.

The duct, the great vessels and all branches must be fully mobilised and controlled before establishing cardiopulmonary bypass. The ascending aorta is usually too small to cannulate, and arterial flow is established by either cannulating the ductus (and then snaring the duct around it) or, more commonly, through an arterial shunt placed on the innominate artery. Venous drainage is usually through a single right atrial cannula.

1. The main pulmonary artery is clamped and transected at the bifurcation. The defect in the central pulmonary arteries is then repaired either directly or with a small patch.
2. If an RV-PA conduit is to be used, the distal end is then implanted onto an opening made into the left or right pulmonary artery (either can be used). The aorta is cross-clamped and the heart arrested. A ventriculotomy is then made in the infundibulum of the RV and the proximal conduit implanted here.
3. The arch is then reconstructed by resecting any coarctation ridge and laying open the inner curve of the small aortic arch back into the aortic root. The arch is augmented

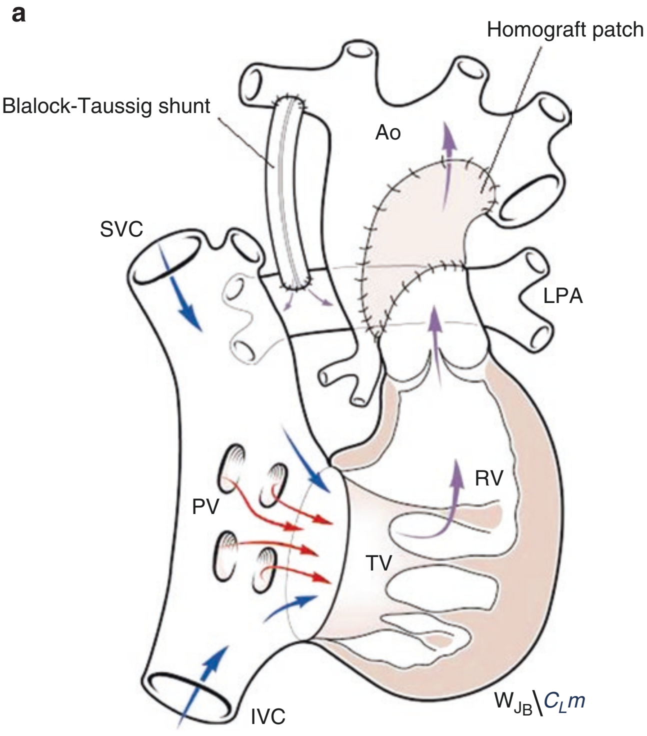

Fig. 102.2 (**a**) The Norwood procedure: the 'classical' technique using a Black-Taussig shunt to provide pulmonary blood flow. (**b**) The Norwood procedure: the 'Sano' technique using a small Right Ventricle–Pulmonary Artery conduit to provide pulmonary blood flow

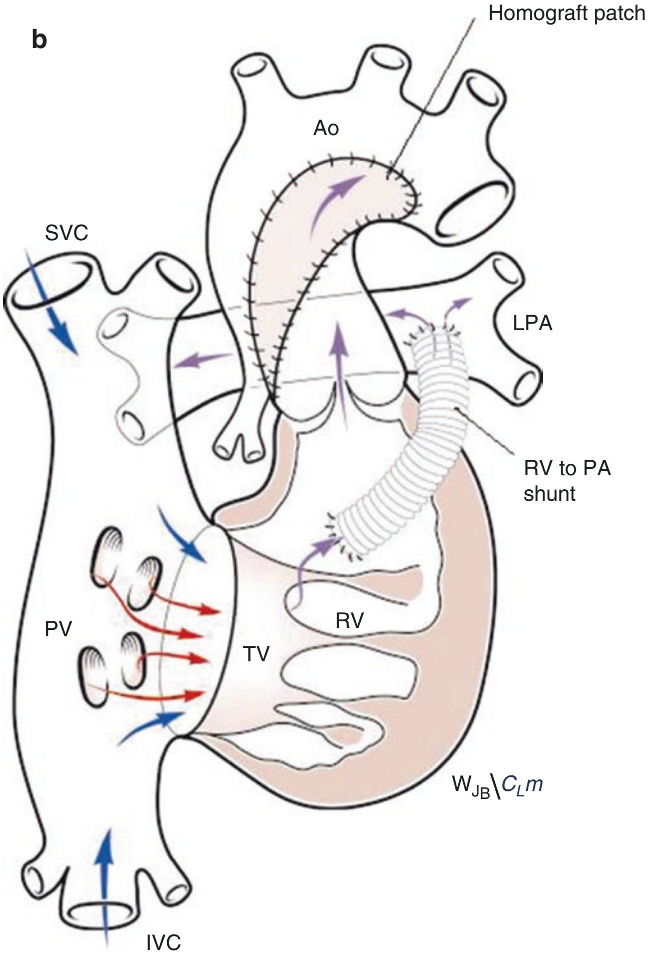

Fig. 2 (continued)

with a patch (typically pulmonary homograft or glutaraldehyde treated native pericardium) and the main PA incorporated into the reconstructed arch (Damus-Kaye-Stansel) to create a composite single outlet to the heart. The arch repair is usually performed utilising a period of deep hypothermic arrest but combined with periods of selective antegrade cerebral perfusion utilising the arterial cannulation of the innominate artery.

4. Atrial septectomy is performed.
5. If a Blalock-Taussig shunt is to be used, then the procedure is completed by implanting the shunt between the innominate artery and the right pulmonary artery. This is usually achieved by moving the arterial cannulation to the (newly reconstructed) aorta and turning down the arterial shunt on the innominate artery (which was used up to this point for arterial cannulation), cutting it to length and implanting the distal end into the right pulmonary artery.

Post-operative management brings together the most challenging areas of neonatal cardiac intensive care with the focus on balancing the systemic and pulmonary circulations. This is summarised in Fig. 102.3 that shows the importance of achieving balance with systemic saturations (SaO_2) in the region of 80% [4]. The immediate post-operative Norwood patient can be one of the greatest challenges to the paediatric intensivist, requiring meticulous attention to ventilatory and circulatory support.

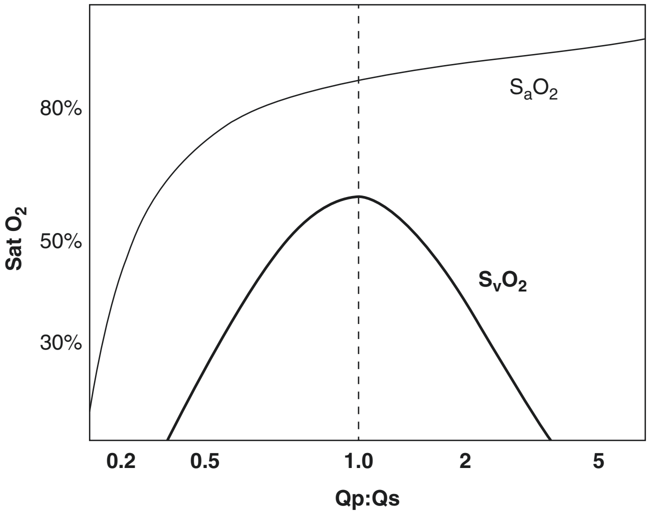

Fig. 102.3 The relationship of arterial oxygen saturations (SaO_2) to tissue oxygen delivery (represented by SvO_2) with changes in the systemic:pulmonary blood flow (Qp:Qs) in the setting of the Norwood circulation

The risk of high FiO_2 or of allowing the pCO_2 to fall is that these may lower pulmonary vascular resistance, volume loading the circulation and leading to cardiac failure. More recently, focus has been more on lowering systemic vascular resistance to secure better systemic perfusion, using vasodilators such as milrinone [5]. Close monitoring of blood lactate and mixed venous saturations help to optimise oxygen delivery and some authors have advocated the use of continuous in-line measurement of mixed venous saturations [6]. The chest is usually left open following these procedures to avoid the compressive effect of the closed chest on right ventricular compliance. The chest is generally closed after 24–48 h on the intensive care unit when haemodynamic stability has been maintained and any tissue and myocardial oedema has resolved. Anticoagulation with heparin is started on the ICU to reduce the risk of shunt thrombosis and this is substituted with low dose aspirin (5–15 mg kg^{-1}) once established on oral feeding.

Right Ventricle to Pulmonary Artery Conduit Versus the Blalock-Taussig Shunt

The Norwood operation was originally described using a BT shunt and arrangement is often referred to as the 'classical Norwood'. A weakness of the BT shunt is that flow occurs throughout the cardiac cycle, creating diastolic run-off away from the aorta that can result in retrograde diastolic flow in the aorta and the risk of coronary steal phenomenon. Patients have a low diastolic pressures and incidences of sudden death where no clear cause can be ascertained even at post-mortem, have been attributed to this. The RV-PA conduit (in the form of a larger simple Goretex® tube of 5 or 6 mm) was proposed as an alternative to the BT shunt as the source of pulmonary blood flow in 2000 by Sunji Sano [7]. The majority of flow occurs in systole and, since there is no run-off during diastole, the diastolic blood pressure is maintained [8]. The more stable post-operative haemodynamics of the RV-PA conduit have made this technique increasingly popular such that is now the dominant type of Norwood performed [9], but only at the cost of a right ventriculotomy-controversy persists as to which technique is best, as discussed below.

The 'Hybrid' Norwood

A third variant in the options for neonatal management avoids the use of bypass completely and aims to achieve similar physiology by securing ductal patency with a ductal stent and placing bilateral bands on the branch pulmonary arteries to control pulmonary blood flow. Balloon atrial septostomy is performed to ensure there is good atrial mixing. This is referred to as a 'hybrid' procedure as it requires a combination approach of interventional cardiology and surgery (Fig. 102.4). The ductal stent can be placed in the operating theatre through a direct purse string, or can be performed as a separate procedure in the catheter laboratory.

This ingenious alternative to conventional surgery has increased in use over the past 10 years but is still only used in the minority of cases. The 'hybrid' procedure has the advantage of avoiding cardiopulmonary bypass, so is particularly attractive in the setting of prematurity, low birth weight or in the presence of an intracerebral bleed or active necrotising enterocolitis (NEC) in which the risks of full bypass and anticoagulation are to be avoided if possible. However, judgment of the bilateral bands is difficult and coronary blood flow remains dependent on retrograde flow from the stented duct, with constant diastolic run-off through the bands, lowering diastolic pressures. Furthermore, the atrial septum or site of ductal stenting can shrink over time necessitating additional interventions or even 'jailing' the proximal arch and so compromising flow to the carotids and coronary arteries. A few centres have adopted the hybrid to replace conventional surgery, but most centres reserve it for very premature or low birth weight babies, or those in whom bypass should be avoided [9, 10].

Outcomes

There is no doubt that this is one of the highest risk procedures in paediatric cardiac surgery. An indication of the risk is reflected in the Risk Adjustment for Congenital Heart Surgery (RACHS) scoring system which allocates a risk weighting to all cardiac procedures and groups the operations according to the perceived risk. The Norwood procedure sits alone in the highest category, Group 6 [11].

Nevertheless, with advances in surgical and intensive care management, the early mortality for the Norwood operation is now 10–15% in most large series. This has to be viewed in the context that this is a universally lethal condition without intervention, but although results have steadily improved over the past 30 years the early mortality appears to be plateauing around this figure. The risk factors for outcome have been extensively studied and a few consistent factors are now well-established, as listed in Table 102.2. Many factors are patient specific and very difficult to influence (such as size of the ascending aorta, tricuspid regurgitation and associated non-cardiac anomalies) although there is good evidence that

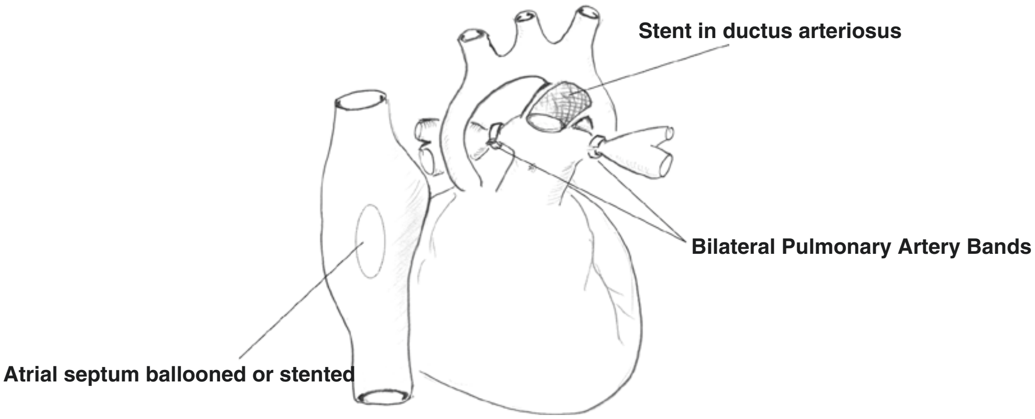
Stent in ductus arteriosus
Bilateral Pulmonary Artery Bands
Atrial septum ballooned or stented

Fig. 102.4 The 'Hybrid Norwood' showing placement of bilateral pulmonary artery bands, a ductal stent and opening of the atrial septum

Table 102.2 Risk factors affecting outcome of Norwood procedure

Prematurity
Low birth weight
Small ascending aorta (<2 mm)
Impaired RV function or tricuspid regurgitation > moderate
Intact or restrictive atrial septum
Associated chromosomal anomalies
MS/AA subtype
Low surgical volume centres

AA aortic atresia, *MS* mitral stenosis, *RV* right ventricle

surgical experience and surgical volume are important factors in achieving better outcomes [12]. However, early mortality is only part of the issue—since there remains a significant attrition in the first few months of life such that 90 day and 1 year survival are probably better indicators of the overall risk of the condition, achieving 70–80% survival at 90 days and 60–70% at 1 year. Interim mortality is high and this remains one of the most challenging areas to improve outcomes, with figures of 4–15% of hospital survivors dying after discharge before the second-stage operation.

A number of patients who are thought to be clinically well at hospital discharge die unexpectedly. Residual aortic-arch obstruction, restrictive atrial septal defects, imbalance of pulmonary and systemic blood flow, diastolic run-off with coronary ischemia, shunt stenosis or thrombosis, and chronic volume overload of the single ventricle have all been implicated as possible causes for interstage mortality. In a post-mortem study, impairment of coronary perfusion (27%), excessive pulmonary blood flow (19%), obstruction to pulmonary blood flow (17%), neoaortic obstruction (14%), and right heart failure (13%) were identified as important causes of interim mortality [13].

The period following stage I is the vulnerable period and it has been difficult to influence the attrition that is seen during this period. The most successful interventions have been the use of home monitoring of pulse oximetry and educating the parents to seek advice if the oxygen saturations fall below 70%. This may help to pick up early signs of respiratory illnesses or the insidious development of shunt stenosis/thrombus. This relatively simple measure has been shown to reduce interim mortality, and in one study eliminated it completely from a previous level of 15.8% [14].

There has been extensive debate regarding the outcomes with the three different surgical options. The RV-PA conduit was introduced to try and address some of the concerns over the frailty of the 'classical' Norwood physiology and there was increasing evidence of the survival benefit of the technique [15, 16] with unequivocal evidence that the aim of improving diastolic pressure is achieved [17]. The Single Ventricle Reconstruction (SVR) Trial was a multi-centre randomised prospective trial carried out over 15 North American centres with 550 randomised patients between 2007 and 2009—an outstanding achievement of cooperation and organisation. The study revealed a 10% survival benefit of the RV-PA conduit over the BT shunt at 6 months [18]. The majority of the benefit appeared to be in the first 60 days following surgery with evidence of better haemodynamic stability as well as overall survival. However, subsequent analysis of the study population has shown that the benefit of the RV-PA conduit becomes less by 5 and 6 years such that there is no significant difference in transplant-free survival between the two groups at 6 years [19]. The post-hoc analyses have suggested that certain morphological subtypes such as aortic atresia groups may particularly benefit from the RV-PA conduit whereas the evidence for surgical experience and case volume show that high-volume centres achieve excellent results regardless of the technique they favour [20]. The pros and cons of the two techniques are summarised in Table 102.3.

Table 102.3 Risks and benefits of the RV-PA conduit Norwood compared to the classical BT shunt Norwood

Benefits of the RV-PA conduit	Risks of the RV-PA conduit
Improved diastolic pressure	Need to perform a ventriculotomy
Lower Qp:Qs Less volume-loaded heart	More interventions between stage I and II
Fewer early post-operative adverse events	Survival benefit not sustained at 5 years
Survival benefit at 18 months	

Comparisons with the 'hybrid' Norwood are more difficult as there have been no such randomised trials. Most centres continue to reserve the hybrid for the most high-risk groups of patients meaning that comparing outcomes with broader surgical series is not valid. Centres who have adopted the hybrid across their entire practice have reported excellent results but direct comparisons remain difficult. In general, outcomes have not been as good as with conventional surgery, but this may reflect the higher risk of the patient groups [21].

Second and Third Stage Procedures

The Norwood operation is the first of three staged procedures that lead to the creation of a Fontan circulation. These are exactly analogous to the staged pathways used in other functionally single-ventricle circulations such as tricuspid atresia or double-inlet left ventricle.

Second Stage

This removes the systemic shunt (whether a BT shunt or RV-PA conduit) and replaces it with superior vena caval flow connected directly to the pulmonary arteries. This is the bidirectional Glenn operation or 'superior cavo-pulmonary shunt' (Chap. 89). The stage II surgery is usually performed at 4–5 months of age. By this age most newborns have doubled their birthweight and the pulmonary vascular resistance has fallen to normal (i.e. adult) levels. The surgery is performed through the same sternotomy incision and using cardiopulmonary bypass. The original shunt is removed, superior vena cava (SVC) is disconnected from the atrium and then connected directly into the right pulmonary artery (Fig. 102.5). Following the Norwood procedure, it is common to see stenoses or tubular hypoplasia of the pulmonary arteries, often related to the site of shunt insertion, and these may need patch enlargement as part of this procedure. It is also essential that the azygous vein is ligated to prevent runoff to the IVC territory. Some cases have bilateral SVC and so require bilateral connections [22]. Most centres perform a standard bidirectional Glenn (as described above) but some will perform the 'hemi-Fontan' which is physiologically exactly the same concept, but where the right pulmonary artery is connected directly into the roof of the atrial mass and the SVC is not disconnected from the right atrium. Instead, a baffle is sewn inside the atrium to commit the SVC flow into the pulmonary arteries, isolating this upper part of the atrium from the main atrial chamber.

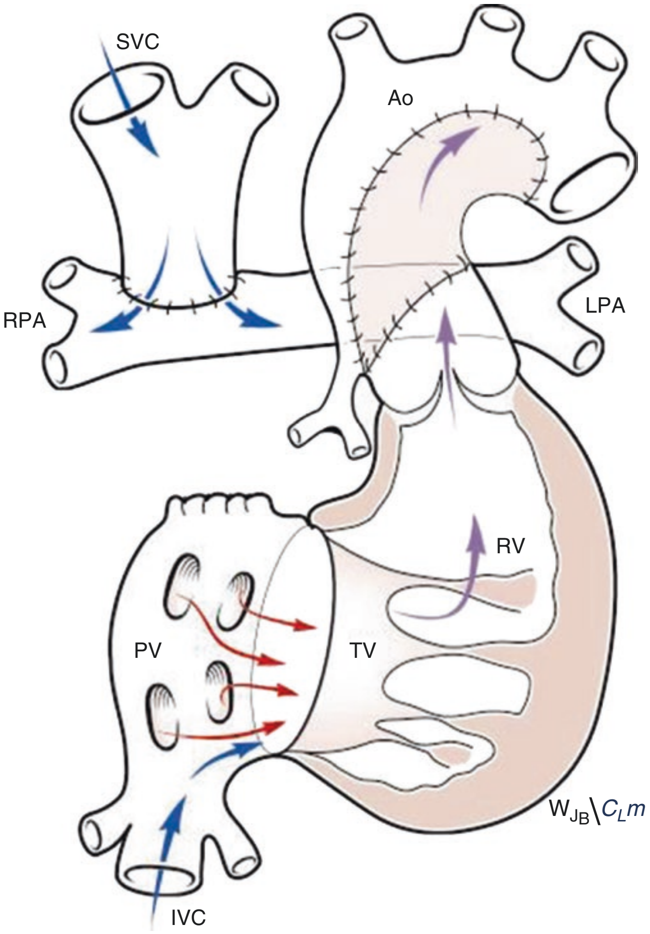

Fig. 102.5 The stage II procedure or bidirectional Glenn (cavo-pulmonary) shunt in the setting of Hypoplastic Left Heart Syndrome

The stage II is a critical step in the pathway, taking the volume load off the circulation and significantly improving the mechanical efficiency of the ventricle. Combined with the older age of the patient and more robust physiology of the infant over the neonate, this is a far lower risk procedure than stage I and generally carries a 96–99% survival.

Completion of stage II is a landmark in the HLHS pathway and patients generally have a far more stable physiology following this surgery. The anastamosis will grow with the patient and saturations are well maintained around 80% with the SVC return flowing passively through the pulmonary circulation. There is little attrition between stages II and III and the timing of the third (and final) stage procedure is partly dependent on institutional preference. Most children will remain well for several years with this circulation. It is only when the child becomes more active and they progress from crawling to walking to running that the amount of inferior vena cava (IVC) return gradually becomes more important and the level of de-saturation becomes gradually more severe—particularly during exercise. Although some centres follow a policy of routinely progressing to stage III surgery at a fixed age (sometimes as young as 18 months) the majority will be guided by patient symptoms and degree of desaturation. This is most commonly around the age of 4–4½ years when the child's activity is becoming limited by desaturation restricting their exercise tolerance.

Third Stage

This is completion of the Fontan circulation. The preparation and technique for the Fontan, or 'Total Cavo-Pulmonary Connection' (TCPC) is essentially the same as for all functionally univentricular circulations. Success depends on well developed pulmonary vasculature, low pulmonary vascular resistance and good ventricular function. Performed on cardiopulmonary bypass, the IVC is isolated from the heart and then routed into the underside of the pulmonary arteries using a Goretex® conduit. This is the extra-cardiac TCPC and is the most commonly performed type of procedure (Fig. 102.6). The alternative is the lateral tunnel TCPC in which the IVC is left connected to the heart, but a baffle is sewn into the atrium to tunnel the IVC flow up into the underside of the pulmonary arteries. Both achieve the same result, with the entire systemic venous return now directed into the lungs under passive flow—a circulation in series rather than in parallel.

It is common to create a fenestration between the two venous circulations (typically 4–5 mm diameter) to act as an escape valve, ensuring good preload for the systemic ventri-

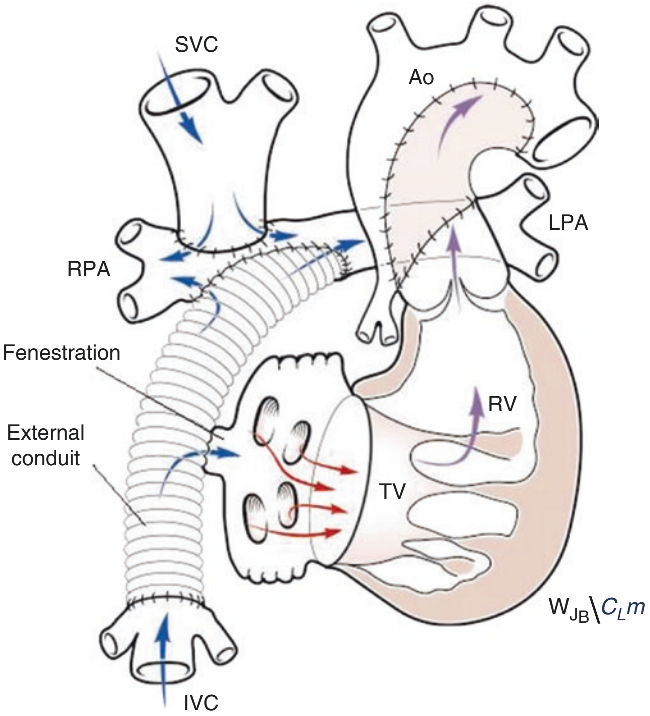

Fig. 102.6 The stage III or total cavo-pulmonary connection in the setting of Hypoplastic Left Heart Syndrome. The diagram shows the extracardiac conduit technique

cle even if there is slow progression of blood through the lungs. The cost of this is a small R-L shunt but gives a more stable circulation. Overall, the stage III procedure is well tolerated and HLHS patients have similar outcomes to those undergoing Fontan procedures for other conditions. Operative mortality is low (2–3%) although there is some evidence that co-morbidities such as prolonged pleural drainage and longer in-patient stay may be higher in the HLHS patients, which may be surrogate markers for a poor-fontan physiology in the future [23, 24].

Late Outcomes

Current data suggest that around 60% of all patients undergoing the Norwood procedure will make it through all three stages with good functional result. Even the oldest surviving cases are still only young adults and so it has been difficult to make categorical assessments of what the future will hold for these patients. The Fontan circulation has its limitations and there are legitimate concerns that a Fontan circulation based on a systemic right ventricle is likely to be at risk of earlier failure than a systemic left ventricle [25], nevertheless the evidence to date suggests that >80% of HLHS patients undergoing Fontan are alive at 15 years, and the systemic right ventricle is not a consistent risk factor in many series [26].

Transplantation

Although neonatal transplantation is a valid alternative approach to the management of HLHS, there are very few neonatal transplant programmes anywhere in the world due to donor availability and the relative urgency of the need for a donor at the point of diagnosis. Loma Linda in the USA has the largest reported experience with a 14% early mortality [27] and multicentre data suggests a further 20–25% mortality awaiting a transplant [28]. In practical terms, the role of transplantation for HLHS has been in the management of patients in older childhood who develop heart failure and are no longer responding to conventional management. These patients are not generally the best candidates for transplantation as they frequently have high panel reactive antibodies from having had previous transfusions and homograft tissue implantations. Older children may also have degrees of co-existing renal or hepatic failure that further compromise suitability for transplant. Long-term mechanical assist devices have shown some promise in 'rehabilitating' these patients to be better transplant candidates.

Future

No other cardiac lesion has received more attention and undergone such changes in management and outcome than HLHS over the past 30 years. Despite remarkable progress, neonatal outcomes have plateaued and the challenge is to further refine techniques and develop bespoke pathways in higher risk cases. The long-term outcome for the systemic right ventricle remains unpredictable and ways of supporting and improving the Fontan circulation will be an increasing challenge in the coming years.

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Congenital Aortic Arch Interruption and Hypoplasia

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Serban C. Stoica

High Yield Facts

- Interrupted aortic arch (IAA) type B is the most common anatomic variant accounting for 70% of cases.
- There is posterior malalignment of the conal septum which contributes to left ventricular outflow tract (LVOT) obstruction.
- Up to 50% of patients with IAA have a 22q11 chromosomal microdeletion and the DiGeorge syndrome.
- The choice of initial procedure is influenced by anatomic features and other non-cardiac factors and it is best individualised.
- Complete repair via sternotomy and with some form of cerebral perfusion is common.
- Recurrent arch obstruction occurs in a quarter of survivors and can be treated surgically or percutaneously.
- LVOT obstruction can be minimised by judicious procedure selection at primary repair.
- If treated primarily or during long-term follow up, LVOT obstruction can be addressed by the Yasui or Ross-Konno procedure or, more commonly, by fibromuscular resection.
- The principles of managing IAA are useful in dealing with arch hypoplasia.

Introduction

Interrupted aortic arch is a rare condition, representing only about 1.5% of congenital heart disease. Without treatment, the outcome is universally poor, with a mortality rate of 90% in the neonatal period. The introduction of prostaglandin E1 (PGE1) treatment allows for temporisation of surgery and optimal perioperative care. Coupled with advances in neonatal surgery, this has led to a dramatic improvement in early results. Long-term however the outcome is influenced by the risk of recurrence as well as problems related to associated lesions, and in particular obstruction in the left ventricular outflow tract (LVOT). In addition, like many children with conotruncal abnormalities, up to 50% of patients with IAA have a 22q11 chromosomal microdeletion and the DiGeorge syndrome. This in itself may cause developmental problems and a reduction in quality of life. This chapter discusses the management of IAA and presents an overview of special situations including arch hypoplasia.

Anatomy

Embryologically the aortic arch has a complex origin and this explains the anatomic variants. In the Celoria and Patton classification, type A interruption is at the isthmus whereas types B and C are in the distal and proximal arch respectively (Fig. 103.1). The most common variant is type B, accounting for 70% of IAA cases [1]. It is exceedingly rare for IAA to be an isolated lesion. Associated abnormalities include ventricular septal defect (VSD) (by far the most common), truncus arteriosus, double outlet right ventricle (DORV), transposition of the great arteries (TGA), aorto-pulmonary window, atrioventricular canal and 'single ventricle'. Some patients have an aberrant right subclavian artery, arising from the descending aorta. This is important for two reasons: it can compress the oesophagus and also indicates that less blood was going through the LVOT in foetal life therefore there is a higher chance of LVOT obstruction after birth. This artery can be divided during the repair if it helps to mobilise the descending aorta. A hallmark of the intracardiac anatomy is the posterior deviation of the conal septum which contributes significantly to LVOT obstruction at presentation or sub-

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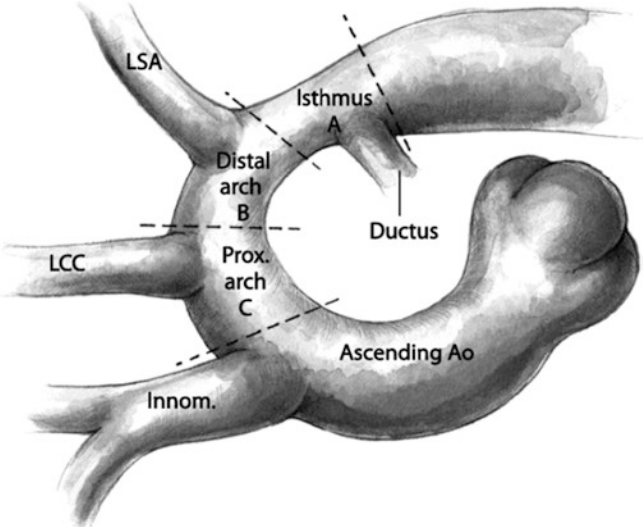

Fig. 103.1 The anatomic segments of the arch and the location of the three types of interruption according to Celoria and Patton. (From Jonas [1], with permission)

sequently. IAA can also be part of a small left heart syndrome across its entire spectrum of severity.

Clinical Features

Changes to the foetal circulation at birth help explain not only the presentation but also some dilemmas related to management. IAA is of little haemodynamic consequence in utero. At birth however perfusion of the lower body depends on the duct remaining open. As the duct starts to close the pulmonary vascular resistance also undergoes physiological changes but the physiological hallmark is impaired or absent perfusion of the lower body. The infant develops acidosis, renal dysfunction and shock. When the ductal circulation is restored the Qp/Qs is variable but generally increased, depending on shunting at VSD level or via associated defects. Antenatal diagnosis allows for a smoother transition to treatment. When IAA is diagnosed after birth, depending on how late this takes place, the clinical signs can range from subtle to dramatic. The distribution of palpable pulses helps determine the anatomic subtype but the mainstay of diagnosis is echocardiography.

Diagnosis and Preoperative Management

In postnatal diagnosis scenarios resuscitation of the child often takes precedence over imaging. A PGE1 infusion is started immediately in a dose of 0.01–0.1 μg/kg/min. Many patients require intubation and circulatory support with inotropes. Once ductal perfusion is re-established, the dose is carefully titrated to avoid steal from the systemic circulation and visceral hypoperfusion. Correction of acidosis and hypocalcemia is also required. A chromosomal analysis by fluorescent in situ hybridisation (FISH) is undertaken. Patients with DiGeorge syndrome are more likely to have hypocalcemia but this can happen in all patients. The DiGeorge syndrome is also associated with impaired T cell-mediated immunity and the risk of graft-versus-host disease. For this reason irradiated blood is used for transfusion, or when the chromosomal status is unknown irradiated blood is used anyway as a precaution based on the IAA diagnosis alone, for example if the infant requires emergency surgery.

Typically the resuscitative measures are successful but complete stabilisation sometimes requires 2–3 days. At this point it is possible to focus on the anatomic detail and define an optimal plan of management. Echocardiography is generally able to offer very good spatial resolution of the IAA itself and associated abnormalities. The position and the length of the aortic discontinuity are described. A detailed assessment of the associated abnormalities is required. The size and the position of the VSD are important surgical considerations, typically the VSD is non-restrictive but occasionally the VSD is small or there are multiple septal defects. The size of the LV and whether it is apex-forming is another key element. The systemic ejection pathway should be carefully evaluated by measurements at the LVOT, aortic valve and ascending aorta level. Colour flow is less useful as only a fraction of the cardiac output is ejected into the aorta. The echocardiographer is almost trying to imagine the ejection pathway after full repair and the key question is if it is anatomically adequate. In this sense absolute preoperative dimensions are more useful and there is a literature on management strategies based on cut-off values for the z score of the LVOT. In generating and interpreting z scores, one should remember that a small measurement error can lead to its further amplification by the regression equations of the z score methodology or the clinical research related to it. As described below, some groups have distilled the collective knowledge in this area and made broad recommendations based on patient size and general principles.

If and when echocardiography is not sufficient to define the anatomy, axial imaging in the form of computed tomography (CT) or sometimes magnetic reimaging is an enormously helpful adjunct. There is less of a place for catheter-based angiography in the setting of IAA, except in very complex variants or in the hybrid situations where it assumes a therapeutic role for ductal stenting. In terms of timing, the simple presence of IAA is a surgical indication as no other treatment is available. The procedure is ideally undertaken when the child is in an optimal condition. Family counselling is an important part of these preparations and it should be noted that in patients with poor prognosis, by virtue of multiple adverse factors, palliative (non-operative) treatment is another pathway which can be explored.

Surgical Management

The treatment philosophy has evolved over the decades. The most common management pathway is complete repair in the neonatal period. Treatment however should be individualised depending on patient circumstances and the need to avoid cardiopulmonary bypass and profound hypothermia. This could be considered in low weight patients or those who have experienced brain haemorrhage, necrotising enterocolitis or need to recover from viral pneumonia. In selected cases therefore a mixture of old and new concepts can be applied in terms of access and staging. Short segments of interruption can be repaired via thoracotomy. If an interposition tube is required this is an elegant solution early on but in the medium term a reoperation is required to upsize it or bring the native tissues together where possible. Left carotid artery turndown bridges the gap with native tissues but at the expense of sacrificing a head and neck vessel [2]. Left to right shunting at VSD level can be dealt with by pulmonary artery (PA) banding which can be done via thoracotomy or sternotomy. Another option to avoid cardiopulmonary bypass is using a hybrid palliation (ductal stenting and bilateral PA bands via sternotomy) [3]. In these scenarios full repair is completed around 6 months of age by VSD closure and PA debanding.

The majority of patients however are strong enough to undergo complete repair, aiming to restore the aortic continuity using native tissues. Typically the VSD is closed at the same time. The arch advancement technique is described next. The same attention to haemodynamics is taken when the patient is transferred to the operating room and during cardiopulmonary bypass. Ideally it should be possible to measure the arterial pressure invasively above and below the IAA. An umbilical line should be kept, if present, if not a femoral arterial line can be inserted. Access is via median sternotomy and the thymus is excised. The arterial cannulation site is carefully chosen. Typically in neonates two 8 Fr cannulas are used to perfuse and cool uniformly the upper and lower body. The innominate artery is cannulated directly or through a 4 mm GoreTex shunt. Alternatively, the ascending aorta is accessed just below the innominate take-off. Both methods allow to perform continuous cerebral perfusion during arch repair. If the aorta is cannulated directly, the cannula can be advanced up into the innominate artery during the central part of the operation (but this may add some clutter to the field) and then withdrawn again into the reconstructed arch during rewarming. A Y connector is used to insert a second arterial cannula in the main pulmonary artery and this can be advanced through the duct. To avoid handling of a fragile duct another option is to leave the second cannula in the pulmonary artery and simply snare the pulmonary artery branches at the start of cardiopulmonary bypass, thus avoiding pulmonary steal; in this case the PGE1 infusion needs to continue throughout the cooling phase. Bicaval cannulation permits intracardiac repair without circulatory arrest and therefore is more commonly done. Many VSDs can be closed via the pulmonary artery and this is compatible with single atrial cannulation. However, as this is rarely known with certainty in advance so bicaval cannulation offers more access options. It also removes the pressure to add more circulatory arrest or low flow bypass for the VSD part of the operation. The heart is usually vented via the right superior pulmonary vein.

During cooling more dissection is carried out, particularly of the descending aorta. When intercostal or mediastinal branches are seen one knows that this is a level beyond any ductal tissue and therefore indicative of where the native aorta starts again. When the aorta is opened the ductal tissue itself has a typical crumbly, soft appearance but this is not universally present. The left subclavian or an aberrant right subclavian artery are divided if it is felt that they add unnecessary tension and the anastomosis is at risk of bleeding or stenosis. These preparations take a while but soon enough the core temperature of 18 °C is reached. In cases where the dissection of the aorta and its branches is not too difficult and is completed from the outset, part of the initial bypass run can be used to arrest the heart and examine the intracardiac anatomy, even commence the intracardiac repair. The aorta is therefore clamped and cardioplegia is given at 18 °C or on the way down. A single dose of cardioplegia is usually sufficient. If multi-dose cardioplegia is used it seems prudent to give another dose if the cross-clamp time is long or if some of the myocardial ischaemic time takes place above 18 °C.

When the target temperature is reached the circulation can be stopped completely or selective cerebral perfusion (SCP) is carried out. The head and neck vessels are occluded proximally and cerebral perfusion is maintained at 20–50 ml/kg/min, targeting a right radial pressure of 30–40 mmHg and physiological near infrared spectroscopy (NIRS) readings. The advantage of complete deep hypothermic circulatory arrest (DHCA) is a less cluttered field, as the aortic cannula can be removed during the repair, and a shorter bypass time overall. Surgeons who choose this option are generally able to complete the arch repair under 30 min. SCP on the other hand allows for an unhurried arch reconstruction in the knowledge that the brain is protected, with further reassurance given by NIRS monitoring. Two trials comparing these bypass techniques however did not show the superiority of SCP over DHCA [4, 5]. In practical terms this remains a matter of surgical preference.

The main step of the repair starts by suture ligating the duct proximally. A C-clamp is placed on the descending aorta. This helps to bring it up into view and also stops any back bleeding if SCP is in use. All ductal tissues are completely excised until the clean, stronger edges of the native descending aorta can be appreciated. Next a counter-incision is made on the proximal aorta. Some surgeons prefer to place this half and half on the ascending aorta and the corresponding head and neck vessel (e.g. in the case of type B interruption that would be the left common carotid). Other authors have a preference for placing this anastomosis very proximally, entirely on the ascending aorta if possible. This too is a matter of judgement but tension on the anastomosis should be avoided at all costs. Supplementing the repair with a homograft patch anteriorly is often a good option to reduce tension. A drawback of a low anastomosis is the potential for this to cause compression of the left main bronchus. This is best avoided by meticulous and extensive mobilisation of the aorta and its branches. Particular care is required to identify and preserve the recurrent and the phrenic nerves. The suturing is typically done with 6.0 or 7.0 prolene in continuous fashion. Some surgeons prefer to use resorbable polydioxanone but this has more tissue drag and there is little evidence that it improves growth of the anastomosis.

When the arch reconstruction is complete, full flow is resumed and attention turns to the intracardiac repair. In the presence of bicaval cannulation rewarming can start as it is unlikely to have to stop the circulation again. If an atrial communication is present this is closed directly or with a patch. Leaving a residual atrial communication risks not giving the left heart adequate preload. The left ventricle has reduced compliance and furthermore can be suboptimal in size, so a left-to-right shunt at atrial level can be significant and haemodynamically deleterious.

Closure of the VSD is done via the tricuspid or the pulmonary valve, depending on its location. If the VSD sutures have to go through the pulmonary annulus great care must be taken not to injure the valve as it may be required for a Ross procedure at a later date. If the conal septum is judged to be potentially problematic for causing LVOT obstruction it can be dealt with in several ways. One option is to incise or excise it carefully as advocated by Suzuki et al. who published good results with this method [6]. Another possibility is to place the patch on the left side of the conal septum thus allowing the pressure in the LVOT to push the upper septum and the patch towards the right ventricle; a key element of this technique is not to oversize the patch to avoid protrusion in the LVOT [7, 8] (Fig. 103.2).

The operation is then completed in the usual fashion. If there is concern about the size of the systemic ventricle or ejection pathway another option is to leave the VSD open at this stage and control the pulmonary flow with banding. When airway compression is a significant concern consideration can be given to aortopexy, where the aorta is fixed to the back of the sternum. Another option is to lengthen the reconstructed aorta with an interposition tube but this is rarely required if the aorta has been mobilised well prior to the repair.

In cases where other anomalies are present these are approached in a logical and systematic fashion based on general principles. For example, the association of truncus arteriosus or TGA adds significantly to the length and complexity of the operation. A good result however can be expected if a complete and accurate repair is achieved. Single ventricle anatomies are managed according to the Norwood principles.

Postoperative Care

At the end of the procedure the transoesophageal echocardiogram assumes an important role. The arch repair is not easily visualised but generally reassurance is provided by the invasive pressure measurement lines in the upper and lower body. The echo focuses on function and makes sure that there are no residual lesions. Ejection via the LVOT is carefully evaluated. The haemodynamics can be fragile after a complex neonatal operation so a low threshold is needed for using optimising manoeuvres in combination, including modified ultrafiltration and leaving the chest open. If the child fails to progress in intensive care the search for impaired haemodynamics continues and this may need cardiac catheterization if echo imaging is not sufficient.

Results

Reports from single institutions have been useful in showing the wider surgical community what can be achieved in terms of strat-

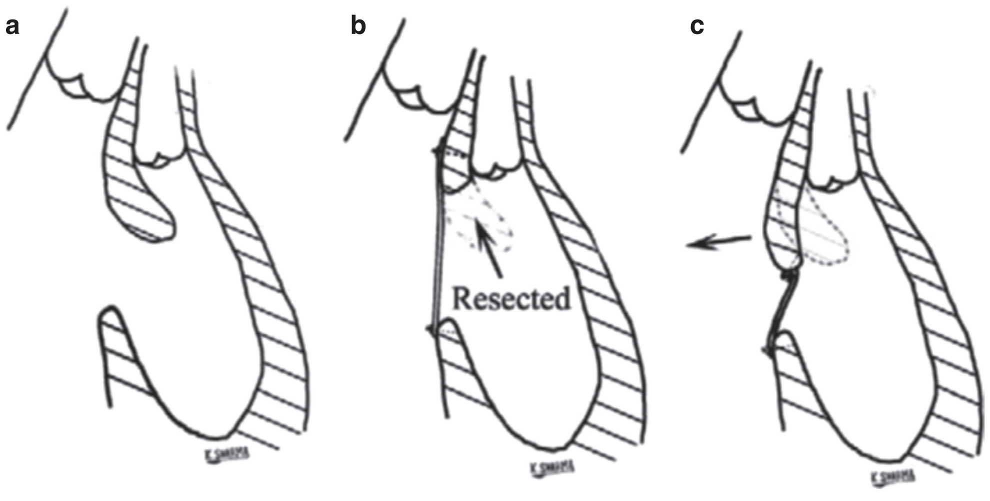

Fig. 103.2 (**a**) Left ventricular outflow tract (LVOT) obstruction caused by posterior malalignment of the conal septum; (**b**) Relief of LVOT obstruction by resection of the conal septum; (**c**) Alternative anchoring of an undersized VSD patch to the tip of the conal septum. (From Tchervenkov et al. [8], with permission)

egies and outcomes. For complex conditions few initiatives provided more useful insight than the Congenital Heart Surgeons Society (CHSS) reports. This academic registry focused on complex pathologies enrolled children at birth and followed them up long-term. The first seminal study on IAA was published in 1994 by Jonas and colleagues [9]. Between 1987 and 1992, 183 neonates were registered with IAA-VSD at 30 institutions and 9 died without surgical treatment. Of 174 patients operated on, the survival was 73% at 1 month and 63% at 4 years respectively. By regression methods the study identified risk factors for death early on and in the medium-term. It could not show the clear superiority of one approach, nevertheless it demonstrated that more patients can have a direct anastomosis via sternotomy (92%) compared to a thoracotomy (26%). Of the patients who do not have the VSD closed at the first operation, typically those treated via thoracotomy, the vast majority require VSD closure within a couple of months. The collective findings of this study gave impetus to the one stage repair philosophy for IAA. It also showed that re-intervention rates are high and LVOT obstruction is a problem in some patients from the outset.

To gather more evidence other patients were prospectively enrolled and another CHSS report followed in 2005 [10]. Of the 472 patients registered between 1987 and 1997 a temporal effect was noticed in that patients treated in the late 1990s had better short and long-term outcomes compared to those born in the 1980s, even though the expanded cohort now included some complex anatomic forms and associations. The overall results are marked by a frequent need for re-intervention in the arch and the LVOT and the impression that IAA is in many respects a chronic disease. By competing risk analysis, over a third of patients survive long-term without any LVOT intervention whereas another third require it from the outset. Of the latter, about a third are alive at 16 years of age without a second procedure and a third require re-intervention with a constant hazard for this. Recurrent arch obstruction, typically defined as a gradient of >30 mmHg, appeared in 23% of patients and was treated by transcatheter or surgical methods in approximately equal proportions. The most recent CHSS report [11] further confirms the chronicity of this condition, with high re-intervention burden and a survival at 21 years of only 60%, with the negative effects most marked in patients requiring multiple re-interventions.

In recent years the early results continued to improve: the Society of Thoracic Surgeons congenital database reports a hospital mortality of only 8.9% in patients operated between 2004 and 2007 [12]. Single-centre series can offer further insight but it should be noted that in all these studies the case mix is an important variable and will affect the figures. One of the largest and most interesting studies is the recent report from Birmingham Children's Hospital [13]. This paper describes 120 consecutive patients treated for IAA between 1988 and 2015. Of these 38 had a VSD, 41 had a Norwood/Yasui-type reconstruction, 24 had truncus arteriosus and 17 had other lesions such as TGA or aorto-pulmonary window—a complex series with IAA as a unifying feature. The main message is that excellent results can be achieved in all groups by using a uniform technique of direct anastomosis augmented by homograft patch reconstruction (Fig. 103.3). Despite the case mix, the mortality was 18.3%

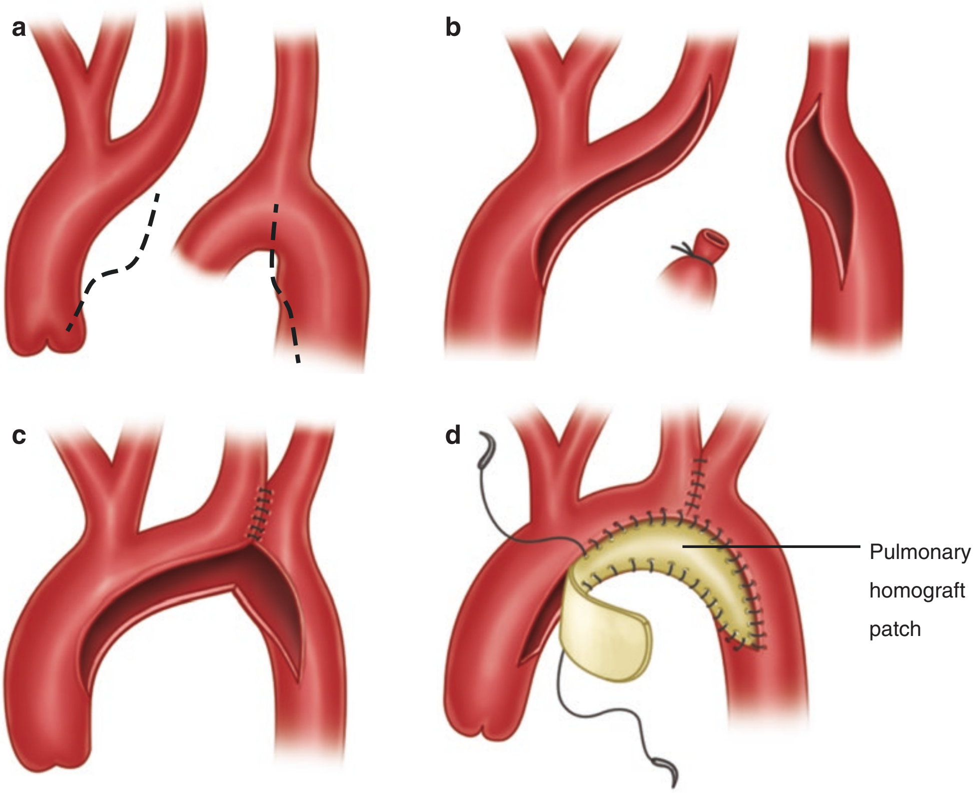

Fig. 103.3 Uniform technique of IAA repair with direct anastomosis and patch augmentation. Example is shown for type B interruption. (**a**) Type B interruption between left common carotid and left subclavian arteries. The dotted lines indicate the surgical incisions made into each component of the arch. (**b**) All ductal tissue excised and both components of the arch opened. The incisions extend into the roots of the head-and-neck vessels. (**c**) Direct anastomosis of the two components of the arch, extending up into the head-and-neck vessels. (**d**) Completion of the repair utilizing a pulmonary homograft patch to augment the concavity of the aortic arch. (From Uzzaman [13], with permission)

overall but only 8.3% for the second half of the cohort. No patients required transplantation and only 10% had surgery for LVOT obstruction, the most common procedure being resection of subaortic stenosis. One patient only had a Ross-Kono procedure and so a low rate of LVOT re-intervention is achievable.

Institutional preference and experience plays an important part in deciding the treatment strategy. For the staged approach it is important to note that some units practise it as a preferred option and the 30-day survival of 95.7% reported by the group in Indianapolis is excellent [2].

In terms of functional status, O'Byrne et al. performed a cross-sectional study of IAA survivors with a median age of 9 years: health status and quality of life were both severely decreased [14]. Joynt and colleagues described detailed neurodevelopmental outcomes 2 years postoperatively and showed subnormal values, with worse outcomes in children with chromosomal abnormalities [15].

Special Situations

Hypoplastic Aortic Arch

This can be a vexing problem which shares many management features with IAA. It is defined in one of three ways: (a) Size of the arch in mm < patient's weight in kg; (b) aortic arch diameter z-score <−2.0; or, (c) ratio of the diameter of the transverse arch to the descending aorta is <50%. Many patients fulfil all three criteria. If echo imaging is inadequate there should be a low threshold for CT which gives good spatial resolution. Some patients have associated coarctation in a periductal location. The key decisions are thoracotomy vs. sternotomy and complete vs. staged repair. An unintended consequence of repair via thoracotomy is moving the obstruction up the arch by the so-called bow stringing effect. This can happen when the narrowest part of the aorta is repairable via thoracotomy but the extended end-to-end anastomosis stretches the more proximal borderline arch which then becomes obstructive. The approach is ultimately individualised based on other cardiac and non-cardiac associated features [16].

LVOT Obstruction

Prior to repair, this problem is best thought of in anatomic rather than physiological terms: the play of pressures across the VSD dictate that a borderline LVOT only becomes obstructive when it accommodates a full cardiac output. Tchervenkov provided an empiric guide on LVOT size in relation to patient weight: (a) if LVOT in mm < weight in kg, survival is unlikely with a conservative approach; (b) if LVOT > weight + 2 then the chances are good; (c) in between these numbers there is a grey area where approach has to be individualised further. At the initial repair the VSD closure can be done in two ways as shown in Fig. 103.2 [8]. In cases where this is not sufficient to generate a big enough LVOT, the VSD is closed to the pulmonary valve and coronary perfusion is ensured by amalgamating the great arteries with a Damus-Kaye-Stansel anastomosis. This is the Yasui procedure, which is completed with a right ventricle to pulmonary artery conduit [17]. Conceptually, it can be pictured as a combination of Norwood and Rastelli.

After the primary repair, development of LVOT obstruction is reported with a variable incidence and its significance is debated. This is also explained by the definition used, where a 'significant' gradient can be described anywhere between 15 and 40 mmHg. Regardless of the definition, some patients require LVOT desobstruction on clinical grounds. The most common procedure is fibromuscular resection. In the presence of a tunnel LVOT obstruction a modified (subvalvar) Konno procedure (septal ventriculoplasty) is a possible option. If the obstruction also involves the aortic valve or its annulus a Ross-Konno procedure is indicated in cases where percutaneous treatment is not suitable. The Ross procedure for this indication has been described in the neonatal period but it is a major undertaking [18]. A critical analysis of LVOT obstruction treated with Ross or Yasui is available on 52 patients from the CHSS database [19]. Recent reports from single centres elegantly showed how judicious initial management reduces the risk of LVOT obstruction in the longer term [13, 20].

Conclusion

Treating IAA is a success story for complex cardiovascular surgery early in life. Good results can be obtained with attention to detail in terms of decision making and surgical technique. There is an important attrition which is more marked if repeat procedures are required in complex anatomic subsets. Focusing on long term outcomes could further improve results in this complex condition.

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Pulmonary Atresia with Intact Septum

104

Imran Saeed

High Yield Facts

- Pulmonary atresia with intact ventricular septum (PAIVS) is a congenital malformation that consists of an atretic pulmonary valve and in which there is no associated ventricular septal defect. This results in high right ventricular (RV) pressure.
- PAIVS accounts for approximately 3% of congenital heart disorders.
- Variable degrees of RV hypoplasia and associated coronary abnormalities affect management options.
- Coronary perfusion may be dependent on flow from the RV.
- Patients usually present with cyanosis.
- Management options include: biventricular, univentricular and one and a half ventricle repair.
- RV size is a key determinant of the choice of surgical strategy.
- PAIVS has a 30-day mortality of approximately 16%.
- Biventricular repair can be achieved in 33–38% of cases, univentricular repair in 17–20%, and one and a half ventricle repair in 5–12%.
- Transplantation is reported in 1–2% of cases.

Introduction

Pulmonary atresia with intact ventricular septum (PAIVS) is a relatively rare congenital malformation that accounts for approximately 3% of congenital heart disease [1]. It consists of an atretic pulmonary valve with which there is no associated ventricular septal defect (VSD).

The aetiology of PAIVS is not fully understood, however, it is associated with variable degrees of right ventricular (RV) cavity hypoplasia as well as coronary artery abnormalities. Hence, a wide spectrum of management options exists, making it one of the more complicated congenital cardiac conditions for decision-making [2].

Anatomy

Overview

The position of the heart and the size of the main pulmonary artery and its branches are usually normal (Fig. 104.1). The pulmonary atresia can be due to an imperforate pulmonary valve membrane (membranous atresia) or due to muscular infundibular atresia (Fig. 104.2).

Right Ventricle and Tricuspid Valve

Estimating the RV size and anatomy is critically important as it guides clinical management. The RV can be classified into three types based on the presence or absence of different anatomic components [2]:

- Tripartite: inlet, apical trabecular and outlet portions present
- Bipartite: inlet and outlet portions present
- Unipartite: inlet portion only present

In general, RV cavity size is largest with tripartite ventricles but gross hypertrophy can result in the obliteration of the different components of the RV even if they are present, and overall outcomes depend more on RV size than on the component parts that are present [2, 3].

The tricuspid valve is usually stenotic and its size correlates with, and is used as an indicator of RV cavity size. Tricuspid valve size is expressed as a Z-score. This represents the number of standard deviations that a value is from the mean (as measured against normative population data) [2].

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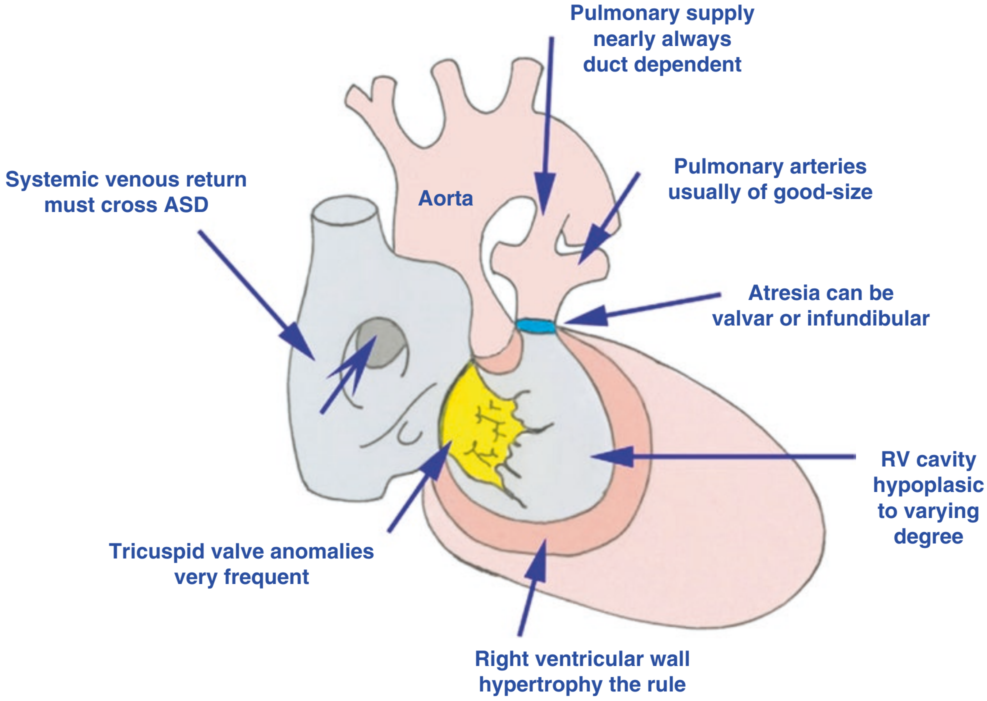

Pulmonary supply nearly always duct dependent
Pulmonary arteries usually of good-size
Systemic venous return must cross ASD
Aorta
Atresia can be valvar or infundibular
RV cavity hypoplasic to varying degree
Tricuspid valve anomalies very frequent
Right ventricular wall hypertrophy the rule

Fig. 104.1 Important features of pulmonary atresia with intact ventricular septum. (Drawing courtesy of Professor Siew Yen Ho, The Royal Brompton Hospital, London)

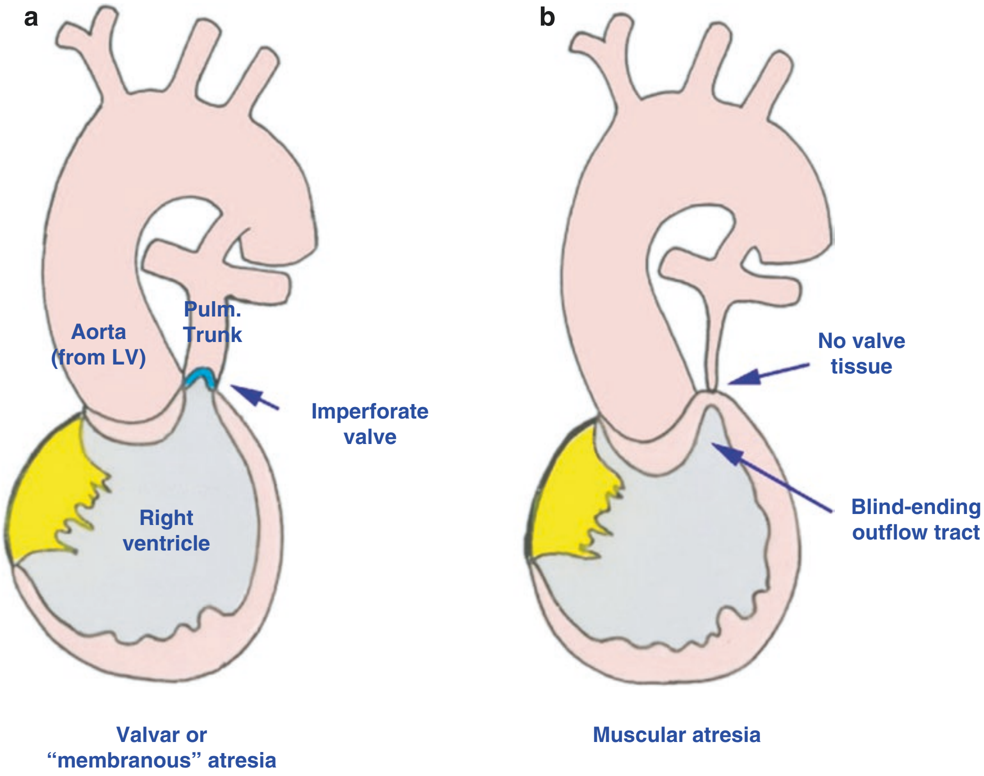

a
Aorta (from LV)
Pulm. Trunk
Imperforate valve
Right ventricle
Valvar or "membranous" atresia
b
No valve tissue
Blind-ending outflow tract
Muscular atresia

Fig. 104.2 (**a**) Membranous and (**b**) muscular atresia. (Drawing courtesy of Professor Siew Yen Ho, The Royal Brompton Hospital, London)

Coronary Abnormalities

Over half of patients have myocardial sinusoids that can end blindly or connect the RV to the coronary circulation. The size and number of sinusoids is inversely proportional to tricuspid valve and RV size [2].

When present, connections between the RV cavity and the coronary circulation are usually to the right coronary or left anterior descending arteries [1]. The relationship between tricuspid valve size, RV morphology and coronary artery abnormalities is shown in Table 104.1.

Table 104.1 Correlations between tricuspid valve size, RV morphology and coronary artery abnormalities[a]

	Tricuspid valve z-score	RV	Infundibulum	Pulmonary valve	RV to coronary connections
Mild	>−2.5	Tri-partite	Well developed	Usually membranous atresia	Major connections usually absent
Moderate	−2.5 to −4.5	Tri-partite or bi-partite RV trabecular component usually absent	Small	Usually membranous atresia	Major and minor connections may be present
Severe	<−5	Uni-partite (diminutive) RV inlet portion present	Absent or diminuitive	Muscular atresia	Major connections common

[a] Adapted from Ref. [4]

In addition, PAIVS is characterised by a high incidence of coronary artery abnormalities. These include abnormalities of origin and distribution, the absence of proximal connections to the aorta (including coronary ostial atresia), stenoses, dilatation and ectasia [1].

Pathophysiology

Blood Flow

The absence of a VSD means there is no outlet for the RV—this results in high RV pressure. In addition, blood cannot pass directly from the RV to the lungs. Hence, an interatrial communication (an atrial septal defect [ASD] or patent foramen ovale [PFO]) is obligatory to allow blood flow into the left atrium and left ventricle. Thereafter, blood reaches the lungs through a patent ductus arteriosus (PDA) as shown in Fig. 104.1.

Right Ventricular Dependent Coronary Circulation

Flow in the coronary circulation can become retrograde from the RV cavity to the coronary circulation. In some cases this high RV pressure can induce coronary artery stenoses such that the usual mechanism of coronary perfusion (aortic diastolic flow) becomes relatively insufficient. The coronary circulation then becomes, at least partly, dependent on high RV pressure—the 'right ventricular dependent coronary circulation' (requiring desaturated RV blood in systole and aortic blood in diastole for coronary perfusion).

In such patients, interventions that decompress the RV can lead to a fall in coronary perfusion, infarction and death [1]. Decompressing the RV has been shown to have 100% mortality in the presence of stenoses in two or more coronary arteries [5].

Presentation and Diagnosis

Patients usually present with cyanosis, are duct-dependent for pulmonary blood flow and require a prostaglandin (PGE1) infusion after diagnosis. In the case of spontaneous duct closure, presentation can be with significant hypoxia and circulatory collapse that requires resuscitative support.

Echocardiography is diagnostic but cannot define coronary anatomy. Hence, cardiac catheterisation and angiography is employed to delineate this either as part of an interventional approach to management (see below) or based on echocardiographic findings (Table 104.1).

Surgical Management

General Principles and Goals of Management

The ultimate goal of surgery is to separate the pulmonary and systemic circulation using the following pathways:

- Univentricular repair (Fontan pathway)
- Biventricular repair
- One and a half ventricle repair

For patients with diminutive RVs the aim is to reach a Fontan circulation where the systemic venous return is directly to the pulmonary arteries. In contrast, the management of the patient with a good size RV is to attain a biventricular circulation where the RV pumps blood to the lungs in the usual fashion.

The eventual pathway to be followed may not be clear for some years, hence, early management usually entails palliative surgical options rather than definitive repair following the principles outlined below.

Stages of Surgery

Neonatal Management

There is no single operation, intervention or defined strategy that caters to all patients. Specific operations or a combination of procedures are individualised according to the patients' morphology and centre preference. However, the management aims at this stage are to:

- Secure pulmonary blood flow with adequate oxygenation
- Relieve RV outflow tract obstruction and decompress the RV (once RV dependent coronary circulation is excluded

or the RV is unequivocally so small that it will not be amenable to future biventricular repair)
- Establish antegrade flow through the RV

Balloon atrial septostomy is considered if the atrial septum is restrictive to ensure that systemic blood flow is maintained.

The above principles can be achieved by catheter intervention or a combination of catheter intervention and surgery or surgery alone. Options include:

- Duct stenting along with perforation of membranous atresia (using wire, laser or radiofrequency) and balloon dilatation
- Catheter perforation and balloon dilatation supplemented by a systemic to pulmonary artery shunt (Modified Blalock-Taussig Shunt [MBTS])

The above principles are usually achieved surgically with:

- Concomitant MBTS, transannular patch and PDA ligation
- Isolated MBTS and PDA ligation

Our preferred approach to MBTS is via median sternotomy (rather than thoracotomy). This approach is technically easier and allows the use of cardiopulmonary bypass if there is any cardiorespiratory instability or if concomitant transannular patching is planned (see below). Table 104.2 outlines some of the key steps when performing the MBTS and Table 104.3 similarly outlines the steps when performing a transannular patch.

Table 104.2 Sequence of steps for performing a modified Blalock-Taussig shunt via median sternotomy

• Resect thymus
• Open pericardium in upper portion only
• Mobilise innominate artery to branching point
• Mobilise right pulmonary artery and PDA
• Test clamp right pulmonary artery for desaturation
• Heparin: 100 units/kg administered
• Bevel proximal end of shunt slightly
• Side biting clamp across innominate-subclavian artery junction
• Arteriotomy and end-side anastomosis (7/0 Prolene™, 6.5 mm needle)
• Side clamp released and shunt flow checked and shunt flushed with heparinised saline
• Shunt clamped: length and orientation to pulmonary artery anastomosis point carefully measured
• Shunt transected transversely at appropriate length
• Distal anastomosis constructed between shunt and right pulmonary artery (7/0 Prolene™, 6.5 mm needle)
• Reduce FiO_2 as clamps removed and shunt opened
• Test occlude PDA and ligate if saturations adequate (≥80%)

PDA patent ductus arteriosus

Table 104.3 Sequence of steps for performing a transannular patch

• Median sternotomy
• Ascending aorta and right atrial cannulation
• Normothermic beating heart bypass or cardioplegia
• Temporary PDA occlusion
• Main PA opened longitudinally crossing the annulus onto the RV by 5–7 mm
• Atretic valve plate incised—opening should allow admission of 6–7 mm Hegar dilator
• Bovine pericardial patch cut to shape over appropriate size Hegar dilator and sewn to main PA
• If saturations adequate can ligate duct
• If concomitant MBTS required do this prior to bypass if possible and occlude temporarily on bypass

MBTS modified Blalock-Taussig shunt, *PA* pulmonary artery, *PDA* patent ductus arteriosus, *RV* right ventricular artery

Management After the Neonatal Period

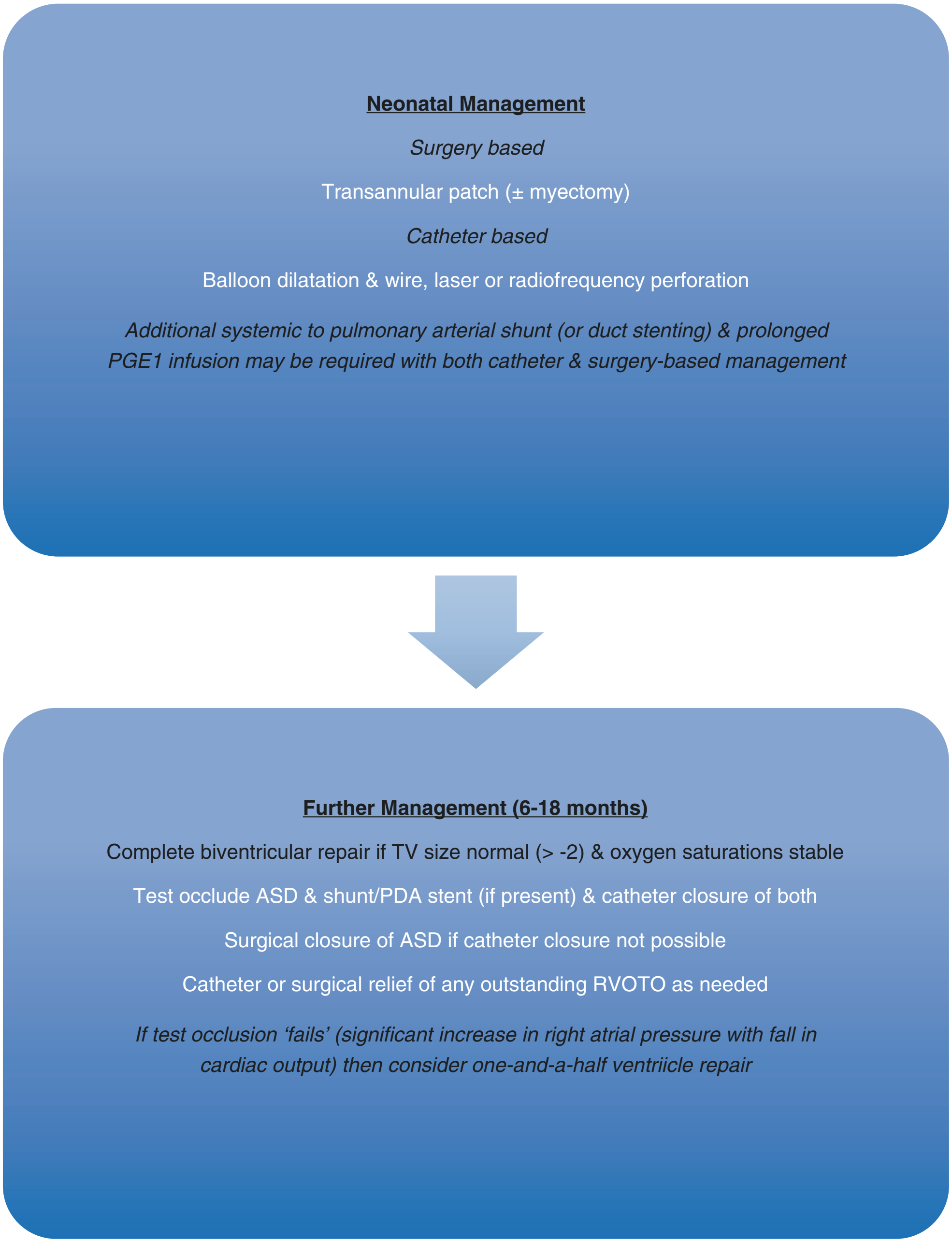
Following the neonatal period, subsequent management is determined by the size of the RV.

Mild Right Ventricular Hypoplasia

Likely management options from the neonatal period onwards are summarised in the treatment algorithm shown in Fig. 104.3.

If at follow-up of 6–18 months oxygen saturations are stable and the tricuspid valve size approaches normality (Z-score of >−2) biventricular repair is usually feasible [6]. If biventricular repair is not deemed feasible following catheter assessment then ‘one and a half ventricle’ repair can be considered.

One and a half ventricle repair involves the creation of a bidirectional cavopulmonary (Glenn) anastomosis and closure of the ASD, as well as taking down any shunts that were performed as part of neonatal management. This approach provides a potentially beneficial ‘halfway house’ between the univentricular and biventricular pathways. In this way, a third to a half of the systemic circulation returns directly to the pulmonary circulation (via the superior vena cava to right pulmonary artery anastomosis) whilst blood arriving from the inferior vena cava is pumped to the lungs. This has the effect of reducing the volume load on the RV as well as decompressing it [6]. The technical aspects of constructing a bidirectional Glenn shunt and Fontan completion are discussed elsewhere in this book.



Neonatal Management

Surgery based

Transannular patch (± myectomy)

Catheter based

Balloon dilatation & wire, laser or radiofrequency perforation

Additional systemic to pulmonary arterial shunt (or duct stenting) & prolonged PGE1 infusion may be required with both catheter & surgery-based management

Further Management (6-18 months)

Complete biventricular repair if TV size normal (> -2) & oxygen saturations stable

Test occlude ASD & shunt/PDA stent (if present) & catheter closure of both

Surgical closure of ASD if catheter closure not possible

Catheter or surgical relief of any outstanding RVOTO as needed

If test occlusion 'fails' (significant increase in right atrial pressure with fall in cardiac output) then consider one-and-a-half ventriicle repair

Fig. 104.3 Management algorithm for patients with mild right ventricular hypoplasia (tricuspid valve Z-score >2). Note that whilst surgery and catheter based interventions are presented separately, a combination of interventions can be used [4]. *ASD* atrial septal defect, *PDA* patent ductus arteriosus, *PGE1* prostaglandin E1, *RVOTO* right ventricular outflow tract obstruction, *TV* tricuspid valve

Moderate Right Ventricular Hypoplasia

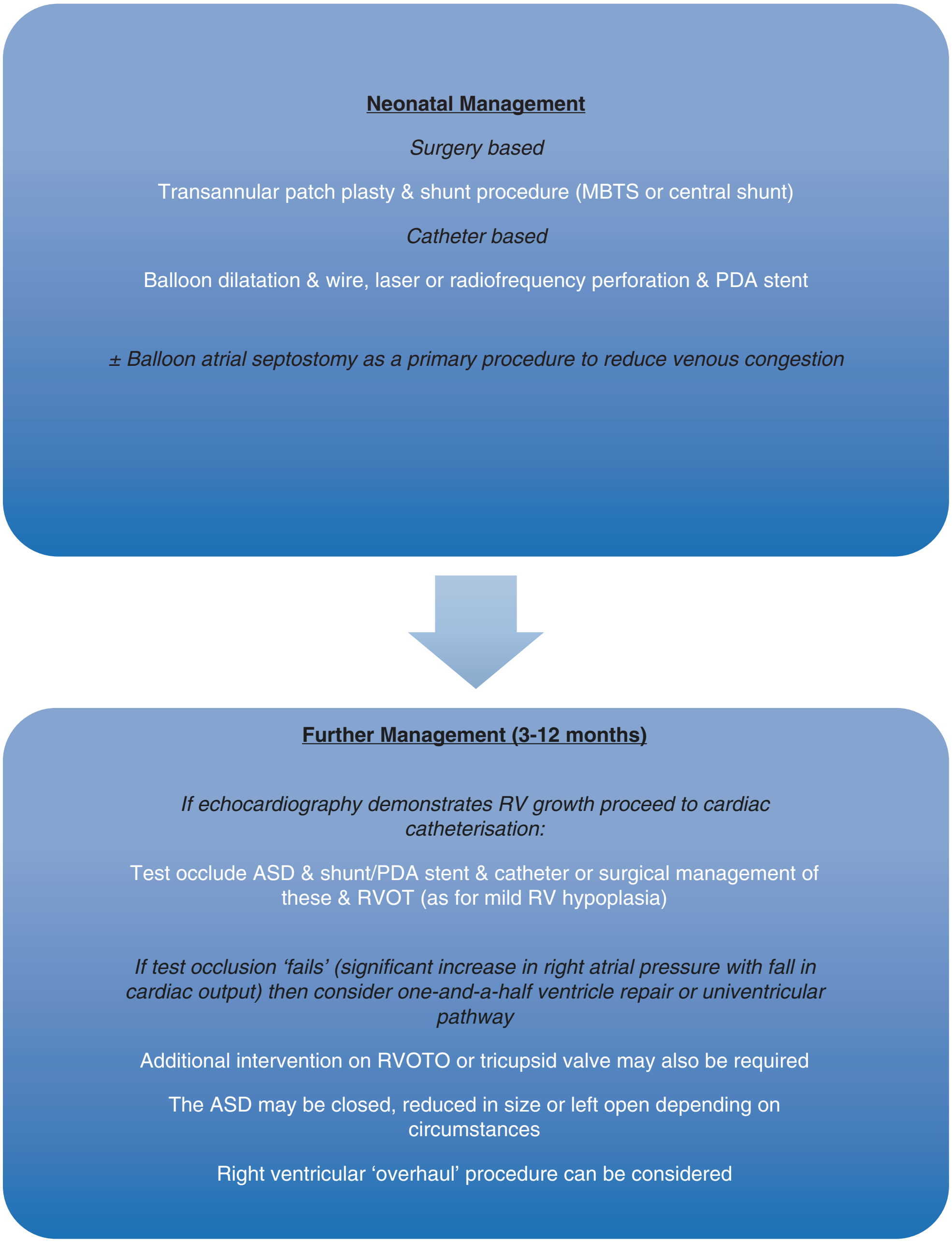
A broad summary of the management possibilities for this group of patients from the neonatal period onwards is shown in Fig. 104.4.

Following the neonatal period this group of patients commonly require additional intervention if a biventricular circulation is to be achieved because of inadequate growth of the RV [4].

A univentricular approach can be also be opted for with takedown of any shunts and performance of a bidirectional Glenn with Fontan completion. Alternatives to following the univentricular pathway at this stage include:

- One and a half ventricle repair (as described above)
- Right ventricular overhaul procedure (in the absence of a right ventricular dependent coronary circulation)

A right ventricular overhaul procedure aims to improve RV capacity and promote right-sided growth, ultimately enabling biventricular repair [7]. The procedure involves RV myectomy with additional procedures undertaken as



Neonatal Management

Surgery based

Transannular patch plasty & shunt procedure (MBTS or central shunt)

Catheter based

Balloon dilatation & wire, laser or radiofrequency perforation & PDA stent

± Balloon atrial septostomy as a primary procedure to reduce venous congestion

Further Management (3-12 months)

If echocardiography demonstrates RV growth proceed to cardiac catheterisation:

Test occlude ASD & shunt/PDA stent & catheter or surgical management of these & RVOT (as for mild RV hypoplasia)

If test occlusion 'fails' (significant increase in right atrial pressure with fall in cardiac output) then consider one-and-a-half ventricle repair or univentricular pathway

Additional intervention on RVOTO or tricupsid valve may also be required

The ASD may be closed, reduced in size or left open depending on circumstances

Right ventricular 'overhaul' procedure can be considered

Fig. 104.4 Management algorithm for patients with moderate right ventricular hypoplasia (tricuspid valve Z-score −2.5 to −4.5). Note that whilst surgery and catheter based interventions are presented separately, a combination of interventions can be used [4]. *ASD* atrial septal defect, *PDA* patent ductus arteriosus, *RVOTO* right ventricular outflow tract obstruction, *TV* tricuspid valve

necessary including: infundibular muscle resection, pulmonary and tricuspid valvotomy.

Severe Right Ventricular Hypoplasia

These patients usually require a shunt procedure or ductal stent (Fig. 104.5) in the neonatal period and are usually directed toward the Fontan pathway. If during the neonatal period decompression of the RV is considered then the presence of a RV dependent coronary circulation needs to be excluded. Cardiac transplantation has also been offered to a small percentage of patients with RV dependent coronary circulations.

Outcomes

Outcomes data for PAIVS are confined mainly to retrospective case series [8]. However, multi-centre registries have shown that PAIVS is one of the premier risk factors for mortality after neonatal MBTS with a 30-day mortality of approximately 16% [9]. This is likely accounted for by diastolic steal and subsequent ischaemia from the susceptible coronary circulation (as discussed above).

Historically, a significant proportion (15–20%) of patients die before reaching a definitive endpoint. Biventricular repair, however, can be achieved in 33–38% of cases, univentricular repair in 17–20%, and one and a half ventricle repair in 5–12%. Transplantation is reported in 1–2% of cases [10, 11].

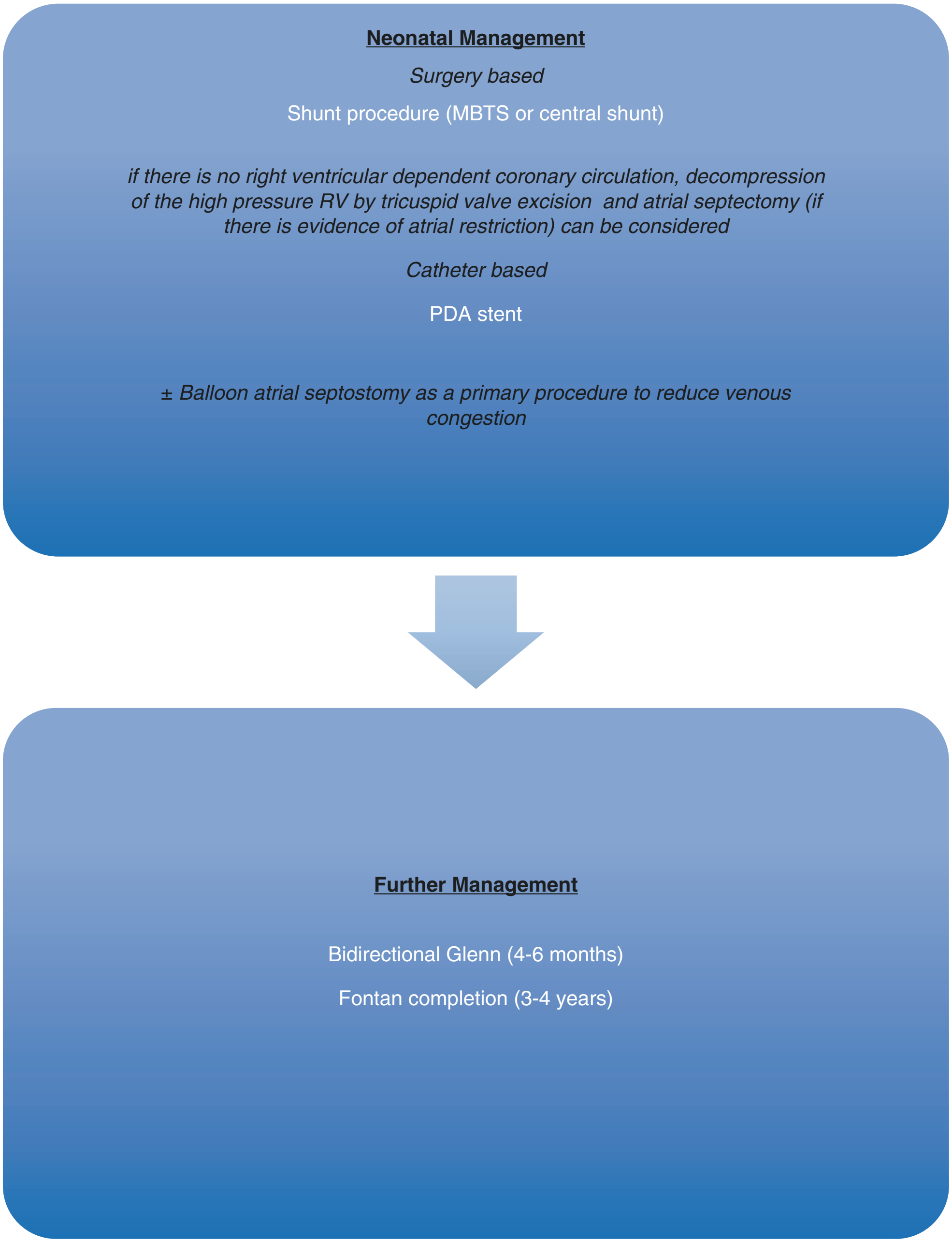

Neonatal Management
Surgery based
Shunt procedure (MBTS or central shunt)
if there is no right ventricular dependent coronary circulation, decompression of the high pressure RV by tricuspid valve excision and atrial septectomy (if there is evidence of atrial restriction) can be considered
Catheter based
PDA stent
± Balloon atrial septostomy as a primary procedure to reduce venous congestion
Further Management
Bidirectional Glenn (4-6 months)
Fontan completion (3-4 years)

Fig. 104.5 Management algorithm for patients with severe right ventricular hypoplasia (tricuspid valve Z-score <5) Note that whilst surgery and catheter based interventions are presented separately, a combination of interventions can be used [4]. *MBTS* modified Blalock-Taussig shunt, *PDA* patent ductus arteriosus

Though overall survival estimates following surgery are variable and often epoch related, 5-year survival of up to 76% and 10-year survival of 80% have been reported [8].

RV overhaul enables early biventricular repair, however, long-term success is limited by the relatively small size of the tricuspid valve as somatic growth progresses [7]. Furthermore, despite the theoretical advantage of biventricular repair, neither biventricular, univentricular or one and a half ventricle repair have been shown to have any clear advantage over each other for exercise capacity, quality of life or survival [8]. This likely reflects the relative size and function of the RV even in those patients who have undergone biventricular repair [12].

The univentricular management route is the preferred route for patients with a RV dependent coronary circulation [13] and RV decompression should not be performed in patients with coronary stenoses in two or more major coronary arteries [5].

Conclusion

Decision making for patients with PAIVS may be complicated, and surgical intervention may be associated with significant mortality. A patient-specific and multi-disciplinary approach to management is required as a uniform approach is impractical because the morphological heterogeneity of the RV makes this impossible.

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Complete Atrioventricular Septal Defect

105

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High Yield Facts

- Atrioventricular septal defect (AVSD) accounts for 2–9% of congenital heart disease, with a prevalence of ~3–5%, and a strong association with Down's syndrome.
- AVSD repair should be performed at 3–4 months of age, although some patients may remain operable until late in childhood. Genotype is not directly relevant to indications or timing for surgery.
- The Nunn technique is preferred for repair of AVSD due to simplicity, reproducibility, and teachability.
- Results in the ECHSA Congenital Database from 2008 to 2018 suggest a hospital mortality of 3.31% for infants 1–12 months age, and for the neonates ~10.26%.
- Surgical treatment has improved the natural history of AVSD.

Introduction

Complete atrioventricular septal defect (AVSD) is a complex and at times challenging congenital cardiac malformation, with multiple co-morbidities and an undeniable learning curve for repair. AVSD accounts for 2–9% of congenital heart disease, with a prevalence of ~3–5%, and a strong association with Down's syndrome. There is interesting historical significance, in that AVSD was the (unsuspected) diagnosis of the first patient operated upon using cardiopulmonary bypass (Clarence Dennis, University of Minnesota, 1951) [1]. Lillehei, Maloney, Trusler, Castañeda, and others made early contributions to our further understanding of the disease and its treatment. As with many congenital cardiac lesions, the full complexity of the anatomy was appreciated only after surgical repair had been realized [2–6]. The Rastelli classification of leaflet morphology set a new standard for surgically oriented anatomic assessment and description [7] (Fig. 105.1). In the current era, intraoperative echocardiographic imaging has evolved to become a sophisticated and essential tool for the repair of AVSD. In this chapter we describe our current thinking regarding timing and technique of repair, with reference to real world expectations for surgical outcome.

Anatomic Features and Nomenclature

Complete AVSD (or the equivalent term "common AV junction") is characterized by absence of the AV component of the membranous interventricular septum [8, 9]. Consequently, both the atrial and ventricular septum are partly deficient, and there is a common AV valve with highly variable leaflet morphology (Fig. 105.1). The Rastelli classification (see below), understood by most cardiac surgeons, is useful in describing the details of the AV valve leaflet arrangement, and facilitates surgical discussion and planning [7] (Fig. 105.2). The AV conduction tissue is displaced inferiorly, outside the triangle of Koch. The ventricular septal component (VSD equivalent) varies as well, from a small communication inferior to the

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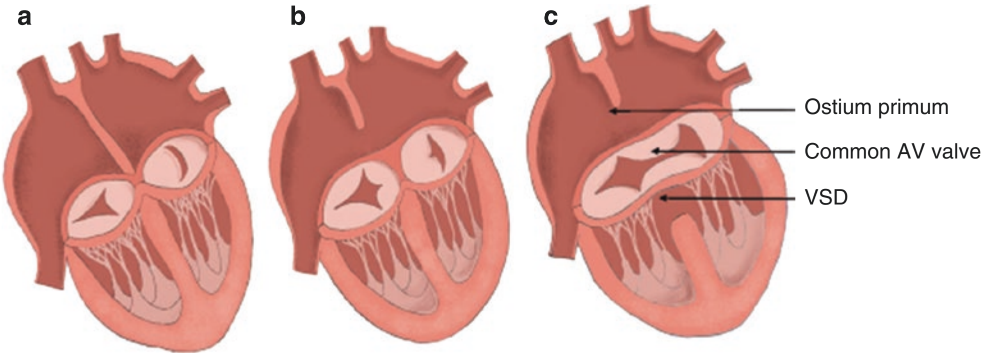


Fig. 105.1 Complete atrioventricular septal defect (AVSD) anatomy (conceptual representation). (**a**) Normal heart with separation of AV valves and intact septa. (**b**) Partial AVSD, or persistent ostium primum, with confluent but separate AV valves and an intact ventricular septum. (**c**) Complete AVSD with common AV valve and absence of portions of ventricular and atrial septa

Fig. 105.2 Rastelli classification of leaflet anatomy in complete atrioventricular septal defect (AVSD) (Types A, B, and C, from left to right). The assignment is based on the degree to which the superior bridging leaflet over-rides the plane of the ventricular septum. In practice, Rastelli B anatomy is quite rare. All cases of AVSD with tetralogy of Fallot have a Rastelli A leaflet arrangement. *SBL* superior bridging leaflet, *IBL* inferior bridging leaflet

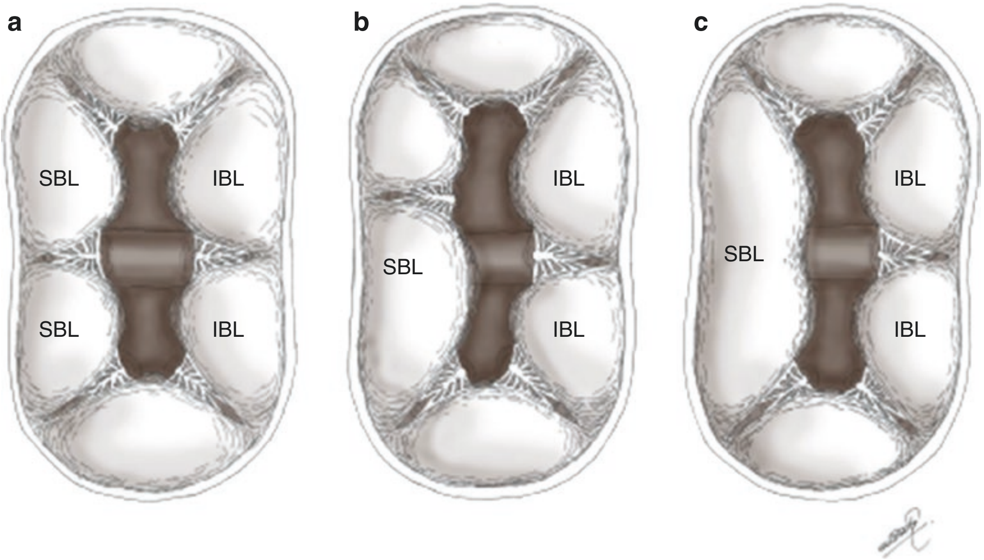
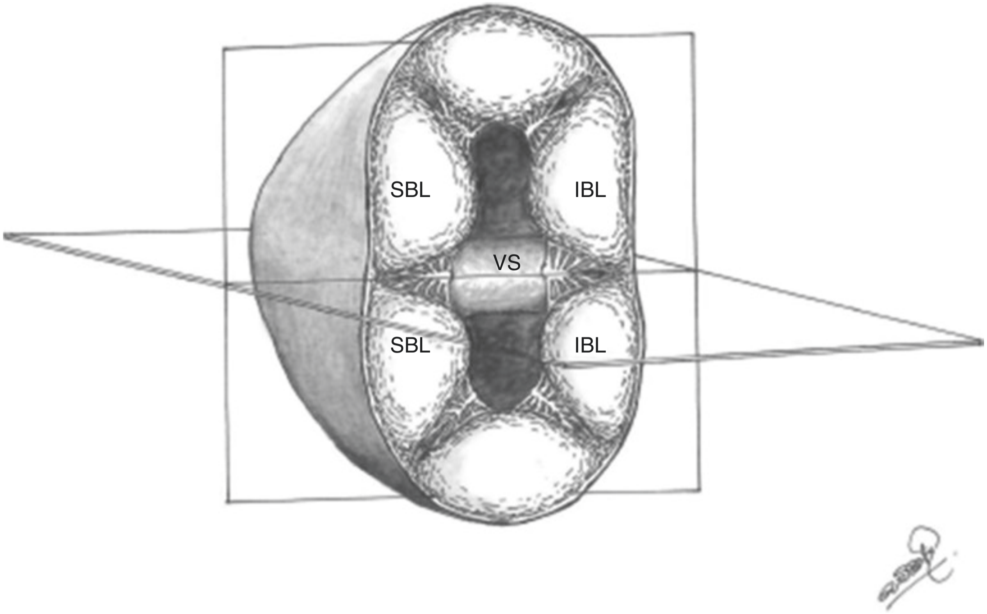


Fig. 105.3 Conceptual diagram of complete atrioventricular septal defect with Rastelli A leaflet arrangement, which may be useful in planning the repair. The plane of the common atrioventricular valve intersects the plane of the atrial and ventricular septal defects. *VS* ventricular septum, *SBL* superior bridging leaflet, *IBL* inferior bridging leaflet. (Modified from Mavroudis and Backer)



bridging leaflet midpoint, to a large semilunar ("scooped") defect spanning the inlet ventricular septum (Fig. 105.2). The atrial defect is usually large and non-restrictive, and confluent with the VSD, with the line of closure of the AV valve components interposed (Fig. 105.3). Cases with a smaller (i.e. pressure restrictive) VSD are sometimes termed "transitional" or "intermediate" AVSD. This does not imply, however, that the VSD anatomy is changing or in transition. In complete AVSD closure of a VSD over time is, in fact, unlikely. Tetralogy of Fallot is an important associated lesion. It is genetically linked to AVSD, and appears in 3–10% of cases. This sort of anatomy usually requires a more complex repair strategy, which lies outside the scope of this discussion [10–12].

Diagnosis

The diagnosis of complete AVSD and all associated anatomic details are usually revealed with 2D (and occasionally 3D) transthoracic echocardiography (Fig. 105.4). Higher levels of imaging (cardiac catheterization, magnetic resonance imaging) are normally reserved for unusual anatomic situations, or (along with other clinical information) for assessment of hemodynamics in late presenting cases, to assess operability. Although not yet widely available, there is interest in 3D reconstruction of computed tomography images and 3D printing to analyze the feasibility and technique of septation. Intraoperative trans-esophageal studies are used to confirm anatomic details and hemodynamics immediately before and after repair, and should be considered the standard of care.

Indications and Timing for Repair

Because there is a strong association of early pulmonary vascular obstructive disease (PVOD) with complete AVSD, "early" repair is usually recommended. The natural history is quite unfavorable, with 80% mortality by age 2 years. However, based on the typical trajectory of the natural history,

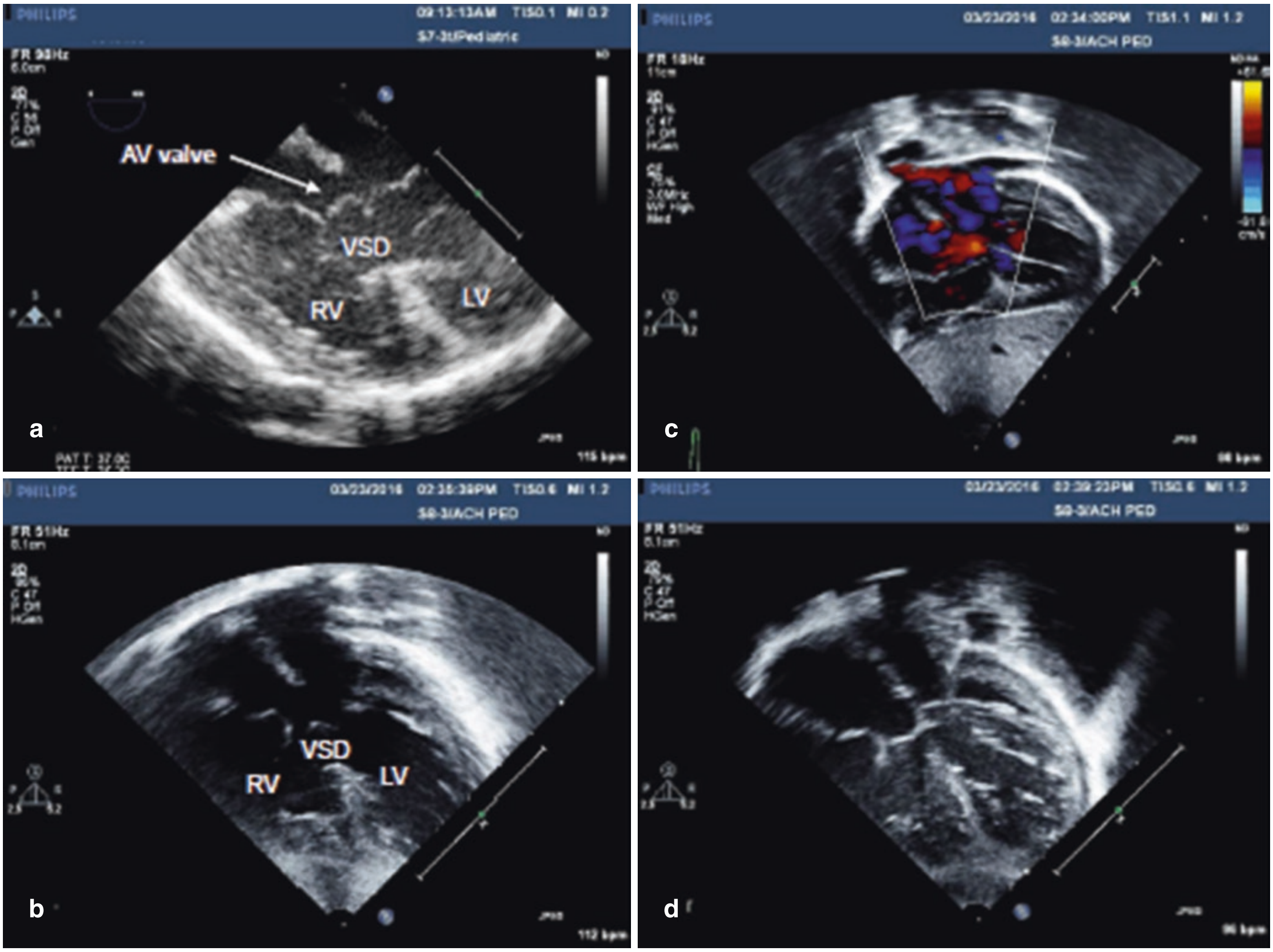


Fig. 105.4 Echocardiographic assessment of an unrepaired complete atrioventricular septal defect. There is a large ventricular septal defect which is confluent with a large ostium primum. There is single large atrioventricular valve with left and right components residing at the same level (without normal offset)

most patients will not require a neonatal operation (neither palliative nor definitive). Although a subject of endless debate, most experienced surgical teams will currently opt for elective repair around 3–4 months of age, striking a balance between maturity of AV valve tissue, tolerance of a complex operation on cardiopulmonary bypass (CPB), and the tendency towards early development of POVD. The arguments against routine neonatal repair are the possibility of residual AV valve insufficiency and ventricular dysfunction, which (especially in combination) may be more problematic for a neonate than for an older infant. On the other hand, failure to thrive, susceptibility to viral pneumonitis, and congestive heart failure are common in AVSD, and may prompt an earlier repair. Curiously, as all teams working in developing countries have recognised, some un-operated infants with AVSD may survive for years, and may even remain acceptable surgical candidates, although this is unpredictable. In the ECHSA Congenital Database, the mean age for repair of AVSD over the past 10 years (excluding outliers repaired after infancy) has been 5.2 months (SD = 2.4, range = 0–12 months).

Specific requirements for repair include balanced right and left ventricular volumes and appropriate AV valve alignment with the ventricles, and absence of advanced PVOD or extracardiac contraindications (e.g. active viral respiratory infection, acute gastrointestinal pathology). Trisomy 21, frequently encountered with AVSD (17–20% of cases), for most surgical teams does not directly affect the timing, indications, and technique for AVSD repair, nor the outcome. Assessment of operability in older patients is highly subjective (and beyond the scope of this chapter), but the *sine qua non* is clinical evidence (physical examination, chest X-ray, echocardiography, and at times catheter-based hemodynamic studies) of a significant left to right shunt.

Babies with severe bronchiolitis and AVSD who fail to improve with medical management (including high frequency oscillation) can sometimes undergo surgical repair with a planned period of veno-venous extracorporeal oxygenation (ECMO) support postoperatively. Other teams may prefer a pulmonary artery band, delaying repair for several months. In our experience it may be quite difficult to calibrate the band to achieve a satisfactory level of palliation in this situation. The effectiveness of the band is diminished in the presence of AV valve regurgitation, possibly due to the increased afterloading conditions imposed on the essentially common ventricle.

General Strategy for Surgical Repair

Repair of complete AVSD can be technically demanding. The Aristotle complexity score is 9 (10 when trisomy 21 is present), and the STAT category is 3 (same as that of the arterial switch operation). The goal is to accurately septate the heart in a way that spares the conduction tissue, and to partition the AV valves with preservation or improvement of valve function.

We have employed several surgical techniques for repair of complete AVSD, conceding that there is probably not a universally applicable or acceptable technique. This is due primarily to inherent variability and complexity of the lesion, as well as local surgical experience. The classically described one and two patch techniques have seen extensive use over the past 50 years, and both seem to work well in the hands of their proponents (Fig. 105.5a, b). Surgeons achieving consistently good results with any available technique tend to be reluctant to change strategies, due to the prolonged learning curve for this lesion. The basic concepts and relative merits of various techniques are presented below, and the reader is referred to other publications for further technical information on the one and two patch techniques [3–6].

Our current preference for repair of complete AVSD is the Nunn repair, which we will discuss in detail [13, 14] (Fig. 105.5c). This technique allows a simplification of the repair via apposition of the AV valve leaflets directly to the crest of the ventricular septum, thus obliterating the VSD and partitioning the common AV valve in one step. The ostium primum is patch-closed separately.

Initially employed in AVSD for small VSD components, the Nunn technique is now used by the authors for most balanced AVSD repairs. The Nunn operation is sometimes (incorrectly and confusingly) called the "modified one patch technique". It is not, in fact, a modification of the latter, but an independent concept. Wilcox et al. and Nunn et al. concurrently employed this technique, but since the latter author published the first large series, the nominal association prevails and is widely understood by cardiac surgeons [13–16]. Although the Nunn technique is also referred to as the "Australian repair", the technique has not been employed consistently Australia-wide, with the majority of cases being performed by teams in Sydney and Brisbane [8].

The Nunn strategy is simple and reproducible, and simplifies some of the critical spatial decision making that is required in other repair techniques.

Minimal manipulation of the valve leaflets is required, especially in Rastelli Type C lesions. No leaflet division is required, and there is a low probability of chordal entrapment and/or distortion. The strategy is conceptually simple, expedient, reproducible, and anatomically sound, combining the best features of prior repair iterations. Most patients with complete AVSD can undergo this type of repair, irrespective of Rastelli type and age (see discussion above). Taken in context, the technique is relatively straightforward to learn and to teach. Although some surgeons consider the Nunn repair to be unsuitable for AVSD cases with a very large ventricular component, others use it non-selectively. Cases of AVSD with tetralogy of Fallot may require individualized

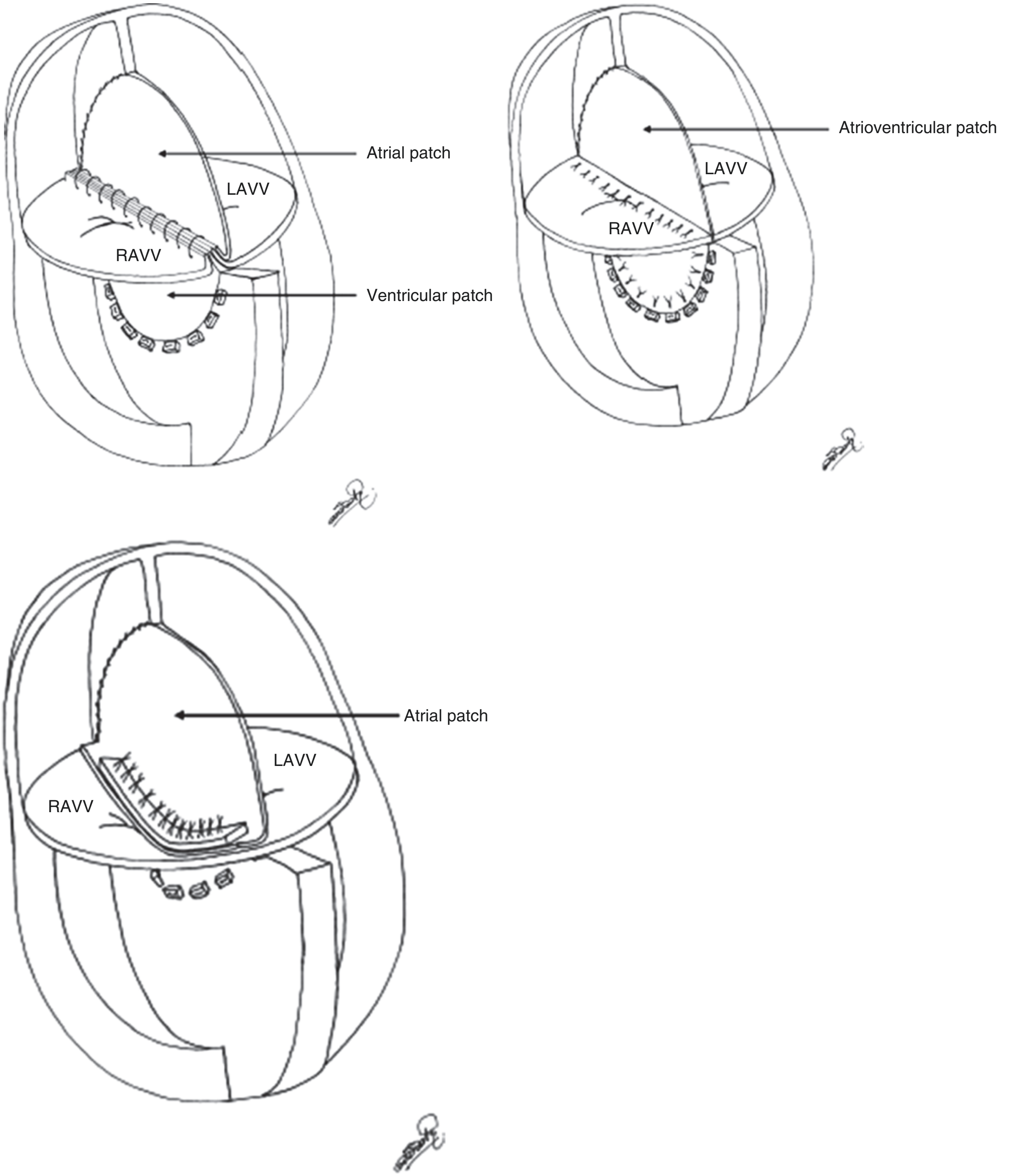


Fig. 105.5 (**a**) Conceptual representation of two patch repair in which separate patches are used for the ventricular and atrial components of the atrioventricular septal defect. No leaflet division is required. The patch is placed beneath the right sided atrioventricular valve chords. The superior bridging leaflet is not incised, and remains anatomically intact. Leaflet dehiscence potential is thereby reduced. This technique may be easier to teach and learn (as compared to the one patch technique). (**b**) Conceptual representation of one patch repair in which a single patch is used to close the atrial and ventricular components of the atrioventricular septal defect. Leaflet division is required for patch placement, and the divided leaflet edges are attached directly to the patch. The patch is placed beneath the right sided atrioventricular valve chords. The one patch technique may provide better exposure of the superior extent of the ventricular septal defect, with some flexibility in the division point of the superior bridging leaflet. (**c**) Nunn repair (authors' preference for most cases) in which atrioventricular valve leaflet tissue is brought down to the crest of the ventricular septum, using a single patch to close the artial component. No leaflet division is required. The chance of leaflet distortion and chordal entrapment is minimized. *RAVV* right atrioventricular valve, *LAVV* left atrioventricular valve

decision making, due to the outlet extension of the VSD in the presence of a small left ventricular outflow tract (LVOT) (see below) [10–12].

Technique of Nunn Repair

The operation is performed via median sternotomy, with standard aorto-caval cannulation (based on patient weight). Full flow CPB at 34 °C and single dose Del Nido cardioplegic solution are used for myocardial and systemic protection, with an expected ischemic time <60 min for most repairs. Modified ultrafiltration is employed following CPB, and for favorable cases, we would plan for endotracheal extubation in the operating theatre whenever possible.

When an arterial duct is present, ligation should be performed at the start of CPB. With the heart in diastolic arrest, the right atrium (RA) is opened longitudinally from the base of its appendage, stopping short of the RA-IVC junction. The anatomy is inspected, and the LV is gently filled with cold saline to assess the line of AV valve leaflet coaptation (Fig. 105.6). To avoid injection of air into the aortic root and coronaries during pressurization of the left ventricle (LV), the cardioplegia cannula is disconnected to allow passive venting. It should be borne in mind that a hand syringe saline injection can easily generate pressure of >200 mmHg, which can damage the flaccid immature myocardium. If the leaflets are not disturbed, they will usually be in coaptation when the atrium is opened, so this step is not always required. With the AV valve leaflets in apposition, the line of septation above the crest of the septum is determined (Fig. 105.7). This line will vary according to leaflet anatomy (Rastelli type). Accuracy of septation will be improved if the apposition point between superior and inferior bridging leaflets is first sutured just above the crest of the septum.

Following this assessment, 6-0 pledgetted polypropylene mattress sutures are placed in the right side of the ventricular septum, away from the septal crest (sometimes as inferior as the base of papillary muscles), allowing an adequate margin to avoid conduction tissue injury. The sutures are brought posteriorly to right sided chords and anterior to chords aris-

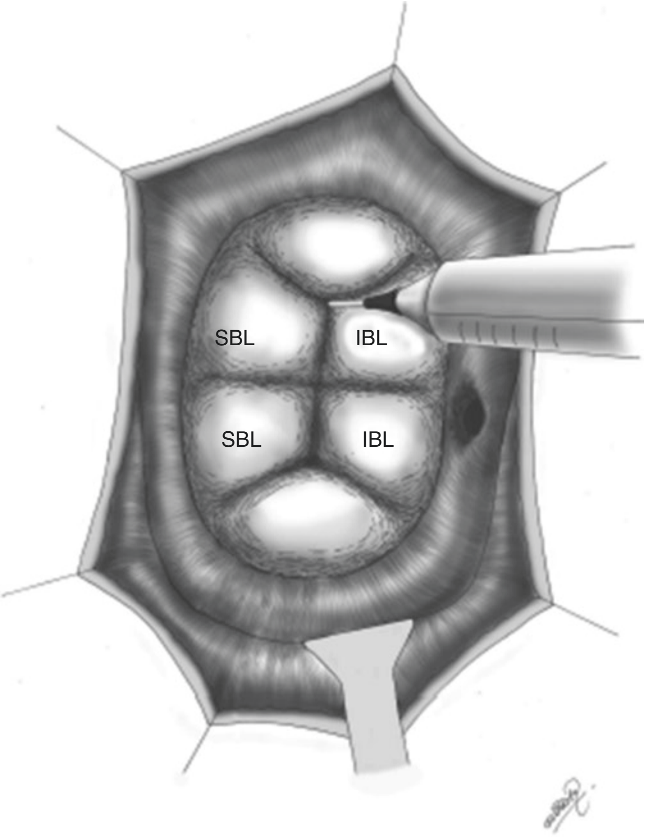


Fig. 105.6 Surgeon's view through the right atrium, showing all leaflets of the common atrioventricular valve (Rastelli type A) in coaptation after a gentle injection of saline. The zone of apposition between edges of the superior and inferior bridging leaflets creates a natural cleft in the septal portion of the left (and sometimes right) atrioventricular valve. *SBL* superior bridging leaflet, *IBL* inferior bridging leaflet

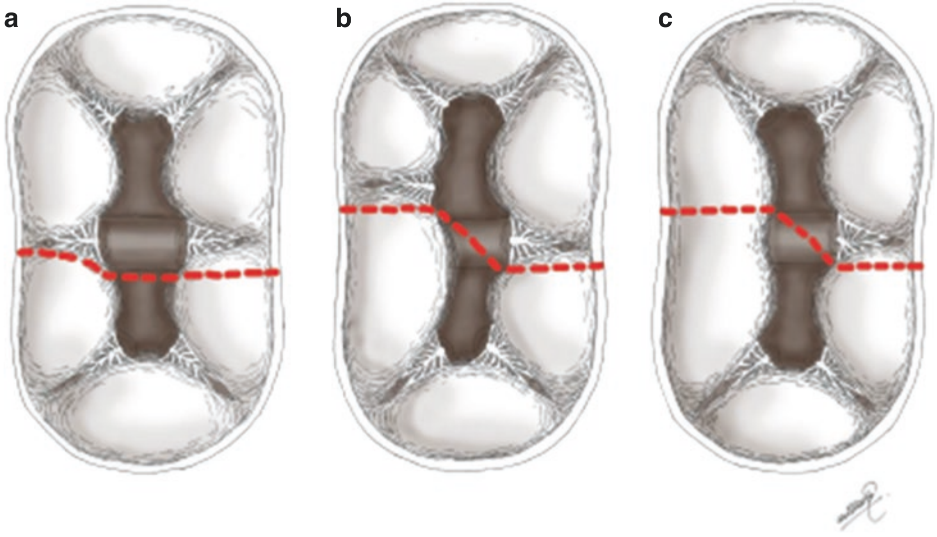


Fig. 105.7 For the Nunn repair, the line of septation of ventricles will vary according to Rastelli leaflet arrangement. From left to right, Rastelli A, B, and C. The broken lines indicate the points at which the leaflet tissue will contact the crest of the ventricular septum, but all sutures are placed on the rightward side of the septum. It is important to leave sufficient atrioventricular valve tissue on both sides of the septum to ensure competence

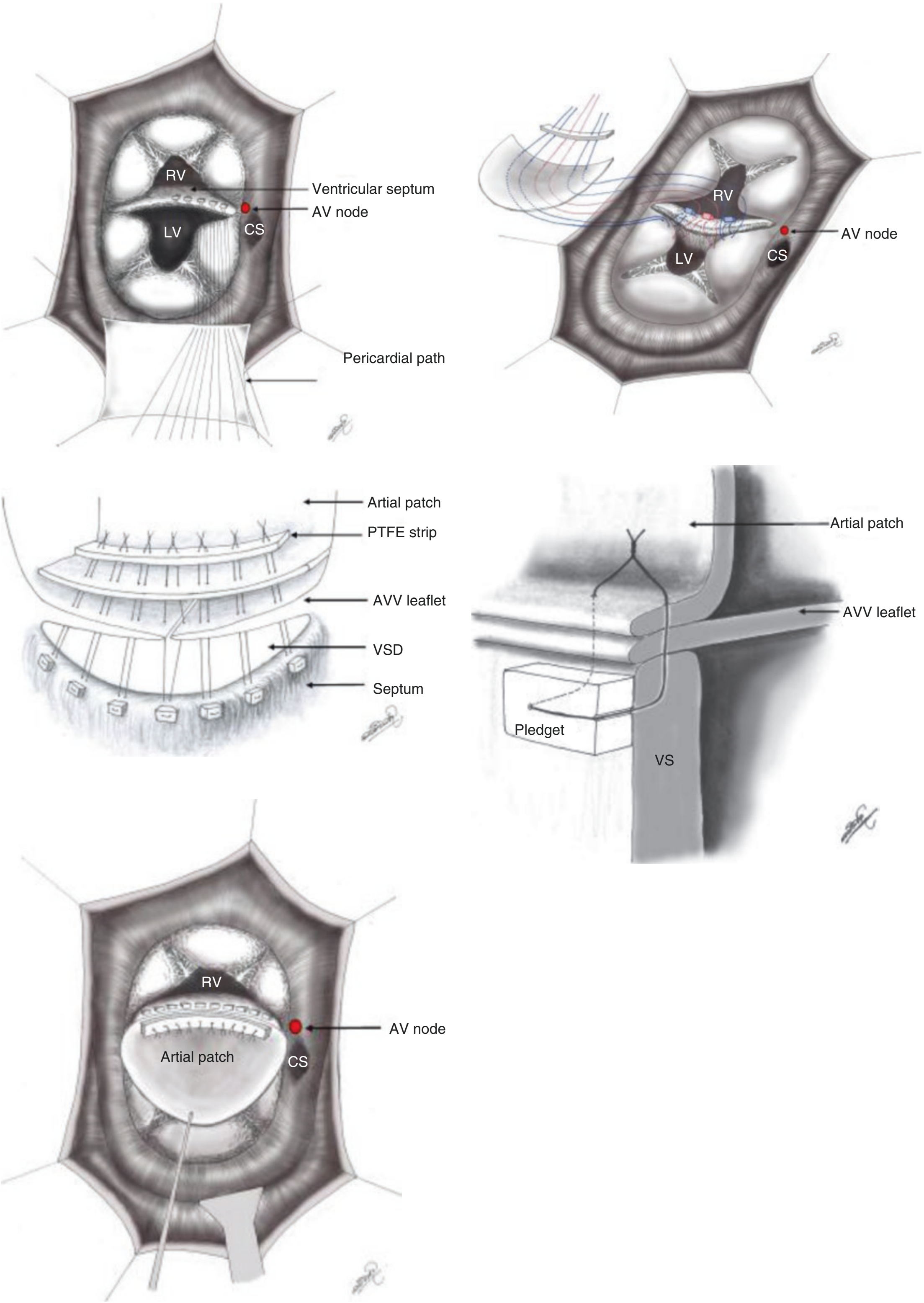

RV
Ventricular septum
AV node
LV
CS
Pericardial path
RV
AV node
LV
CS
Artial patch
PTFE strip
AVV leaflet
VSD
Septum
Artial patch
AVV leaflet
Pledget
VS
RV
AV node
Artial patch
CS

Fig. 105.8 (**a**) Sutures are placed rightward to the crest of the ventricular septum, avoiding the conduction tissue, and then brought through the base of the atrial patch. Shown here is Rastelli A leaflet arrangement. (**b**) In some cases a PTFE strip is used to reinforce the line of patch attachment. The strip length is slightly shorter than the actual transverse valve dimension in order to create an annuloplasty effect. (**c**) Detail of suture placement en face, with sutures placed in right side of ventricular septum, through atrioventricular valve tissue, pericardial patch, and PTFE strip. No ventricular patch is required. (**d**) Further detail of superior suture placement for the Nunn repair. Inferiorly the sutures are kept further away from the septal crest to avoid conduction tissue. (**e**) Completed closure of ventricular portion of atrioventricular septal defect (Rastelli A leaflet arrangement) using the Nunn technique. The atrial patch has been trimmed to correct size, and will remain to the left of the coronary sinus, keeping the latter in the right atrium. *cs* coronary sinus, *LV* left ventricle, *RV* right ventricle, *AV* atrioventricular, *AVV* atrioventricular valve, *VSD* ventricular septal defect, *VS* ventricular septum

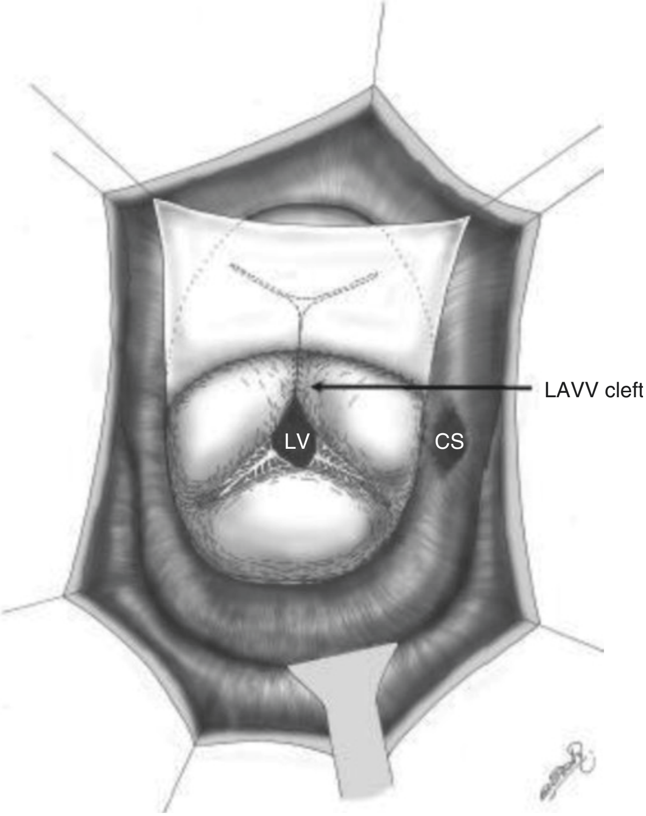


Fig. 105.9 Details of closure of the zone of apposition (cleft) in the septal leaflet of the left atrioventricular valve, using interrupted 6/0 polypropylene sutures. The leftward extent of the closure (i.e. toward the leading edge of the leaflet) is determined by the points of chordal attachment as well as competence testing. *cs* coronary sinus, *LAVV* left atrioventricular valve, *LV* left ventricle

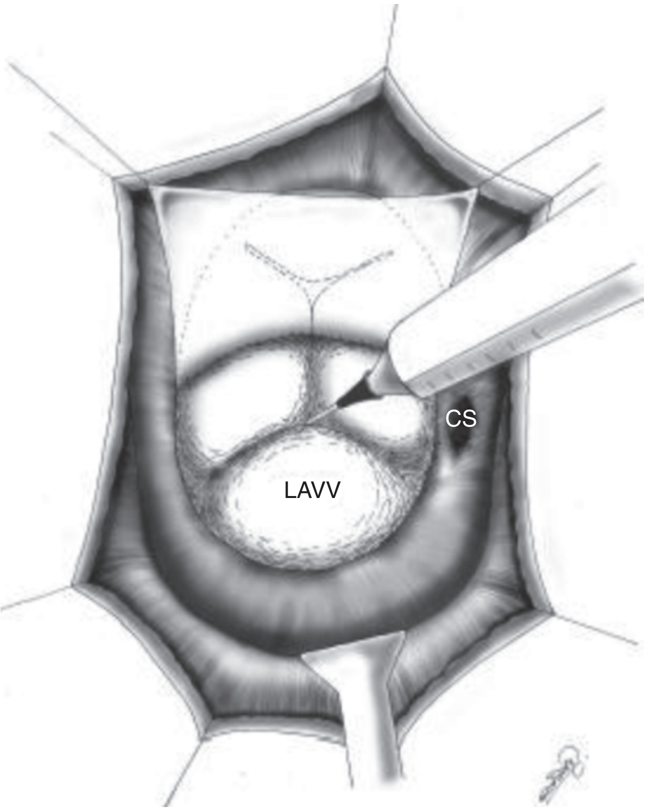


Fig. 105.10 Further competence testing of the left atrioventricular valve (LAVV) following septation. Care must be exercised to prevent over-pressurization of the cardioplegic left ventricle. This exercise will provide information regarding potential or gross leakage points in the left AV valve which may require adjustment. However, full assessment will await transesophageal echo assessment following separation from cardiopulmonary bypass, as the contribution of muscular tensor apparatus to valve competence in the beating heart is important

ing from the crest of the septum, and through leaflet tissue in the proposed line of septation. The sutures are then brought through the base of an appropriately shaped atrial patch, cut from either autologous pericardium or CardioCel® membrane (Admedus, Western Australia) (Fig. 105.8a). This area may be reinforced with a strip of PTFE if autologous pericardium is employed (Fig. 105.8b). In either case, the sutures should be spaced over a shorter distance on the atrial patch than on the septum (about 80%), to achieve a medial annuloplasty effect (Fig. 105.8c–e). After the sutures are tied, the left AV valve is tested for competence and orifice size using gentle pressurization with saline and Hegar dilators. Irrespective of degree of competence, the zone of apposition (cleft) in the septal leaflet of the left AVV is closed with interrupted or layered continuous 6-0 or 7-0 polypropylene sutures, out to chordal attachments points, followed by repeat coaptation testing (Figs. 105.9 and 105.10). Most AV valves will appear competent at this point, but if not, some minor adjustments may be possible (tightening commissures, adjusting leaflet height by chordal plication to papillary muscle heads, stabilizing the annulus). Divided superior or inferior bridging leaflets demonstrating prolapse can sometimes be attached to the corresponding leaflet along the septum to correct this issue. Knowing the mechanism of incompetence at this point is critical, and is based on location of regurgitant jets, leaflet motion, prolapse, residual cleft, accessory orifices, etc. These features, unfortunately, may be difficult to assess in an arrested heart, as the saline test is neither fully sensitive nor accurate. Moreover, many of the valuable techniques available for mitral repair in larger patients are of limited use for small fragile AV valves in neonates and infants with AVSD. The surgeon should concede that gross incompetence at this point may represent inaccurate septation, committing too much of the bridging leaflet tissue to the right AV valve, and must consider revising the basic repair. Most surgeons will acknowledge that competence of the left AV valve is often the prime factor in determining outcome of the repair.

Atrial septation is completed with a running suture around the ostium primum, leaving the coronary sinus in the right atrium. In the coronary sinus area, the suture line

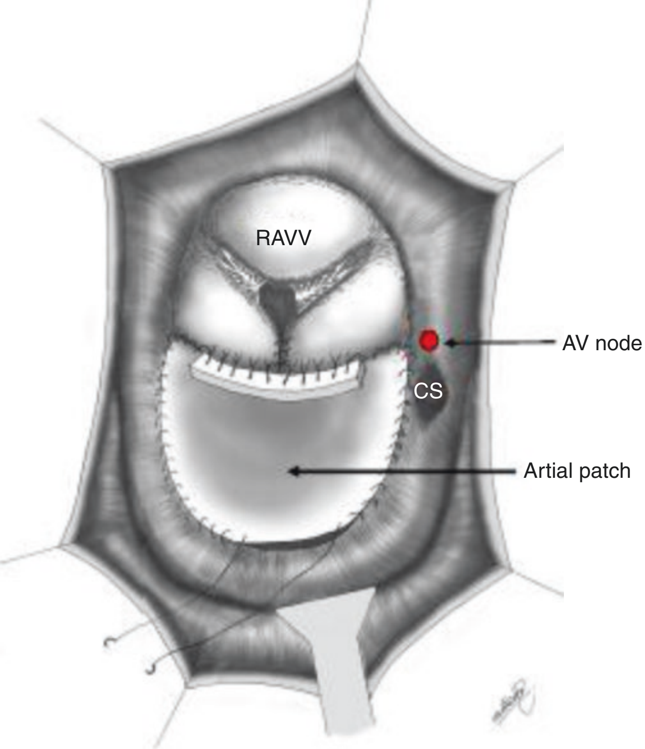


Fig. 105.11 Atrial septation using a pericardial or Cardiocel patch, Rastelli type A leaflet arrangement. The running suture line continues around the rim of the ostium primum. Inferiorly, the line deviates toward and into the left atrioventricular (AV) valve annulus to avoid the AV node. The coronary sinus therefore remains in anatomic position on the right side of the septum. *cs* coronary sinus, *RAVV* right atrioventricular valve

is deviated toward and into the left AV valve annulus, to avoid conduction tissue (Fig. 105.11). Alternately, the coronary sinus can be translocated to the left atrium by deviating the suture line around it anteriorly, rather than between the coronary sinus and left AV valve. Following atrial septation, the right AV valve is assessed in a fashion similar to the left. There may be a cleft effect on the right side of the valve partition, which usually can be closed to improve leaflet apposition (Fig. 105.11). Leakage may also occur if too much AVV has been committed to the leftward orifice. In such cases the orifice is usually of adequate size, and a partial De Vega annuloplasty can be performed, with sutures brought out through the RA wall and controlled with a tourniquet. In this way the annuloplasty can be adjusted as needed after separation from CPB (Fig. 105.12).

The patient is warmed and weaned from CPB, and subjected to modified ultrafiltration to remove the CPB priming volume and also the volume of concurrently administered blood products. Electrocardiogram at this point usually shows sinus rhythm, often with first degree AV block and an incomplete right bundle branch block. Any higher-grade block is treated with temporary AV sequential pacing. Inodilator support is begun and usually maintained for 24–48 h. Complete echocardiographic assessment (transesophageal or epicardial) is performed (Fig. 105.13). Residual shunts should be dealt with aggressively at this point, as they may be poorly tolerated, especially if there is significant AV valve incompetence. Small shunts typically will be the focus of much attention in the intensive care unit, and are often (incorrectly) blamed for any postoperative issues, related or otherwise. Any evidence of pulmonary hypertension, in the absence of residual intracardiac shunts, is treated with nitric oxide delivered through the ventilator circuit, which is the only consistently effective non-invasive therapy. If the latter is not available, creation of a small interatrial communication may be useful in the setting of high pulmonary pressure, accepting some possible decrement in SaO_2. Major issues aside, and with appropriate anesthetic management, endotracheal extubation can and should take place in the operating theatre or shortly after arrival in the intensive care unit for many patients, with a margin of safety.

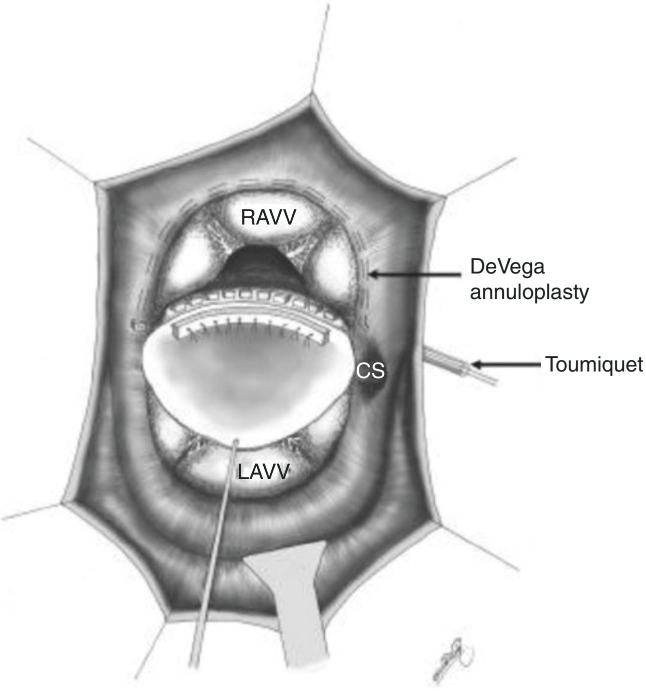


Fig. 105.12 A modified DeVega annuloplasty has been placed around the right atrioventricular valve (RAVV) and the limbs of the suture have been brought outside the right atrium posterior to the cavo-atrial junction. The annuloplasty can be adjusted (if needed) after separation from cardiopulmonary bypass, using echocardiographic guidance. *LAVV* left atrioventricular valve

AV valve competence may change (usually for the better) as ventricular function and/or AV conduction improve, especially during modified ultrafiltration. However persistent high-grade incompetence requires a return to CPB for

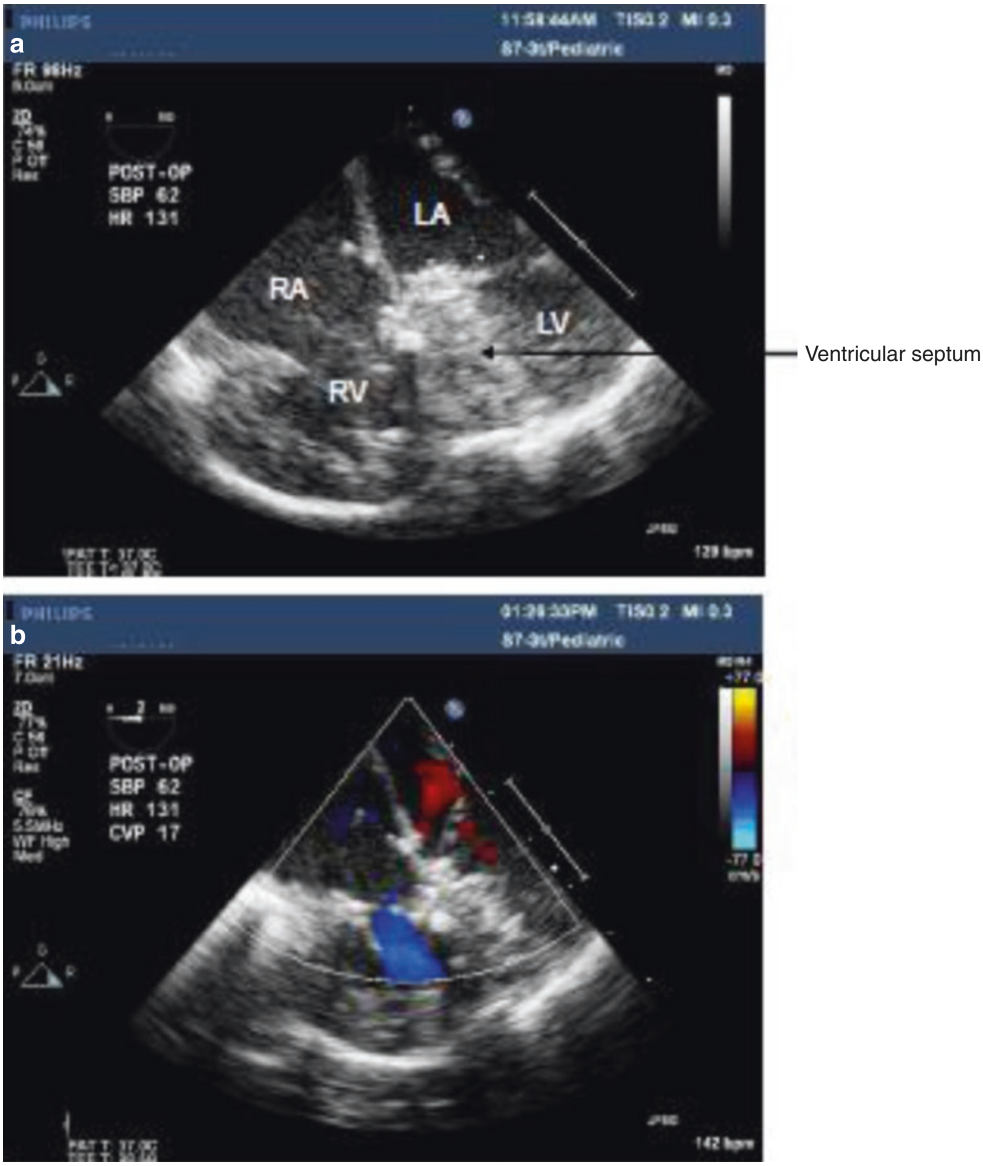


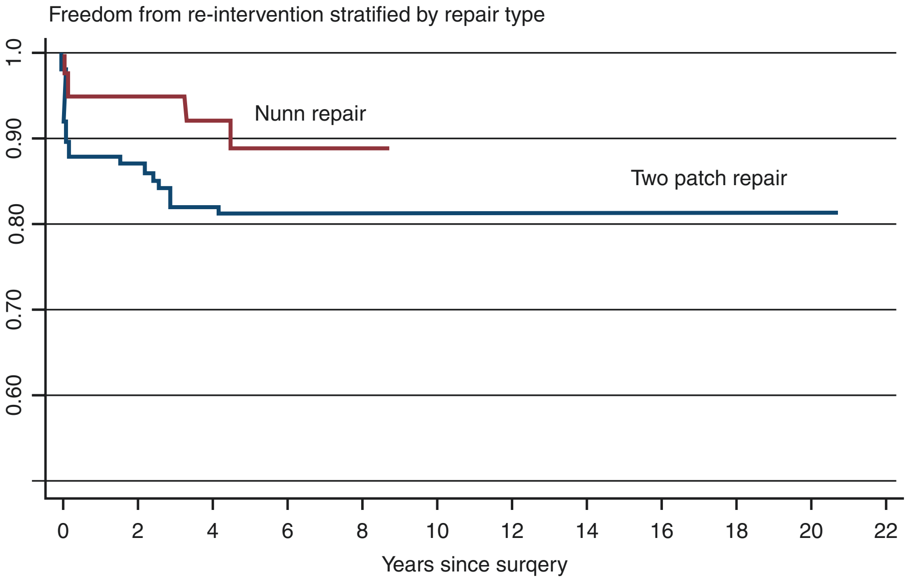
Fig. 105.13 Post cardiopulmonary bypass intraoperative transesophageal imaging is performed to assess the Nunn repair. If unavailable, or if the baby is too small for the available probe, epicardial imaging can also be employed. Assessment of adequacy of septation, valve function, and contractility are critically important at this point. The atrioventricular valve (AV) leaflets have been attached to the ventricular septal crest, eliminating the ventricular septal defect. The atrial septal defect has been closed with a patch. The AV valves are competent and unrestrictive. *LA* left atrium, *LV* left ventricle, *RA* right atrium, *RV* right ventricle

revision after the mechanism is determined. While minor AV valve leaflet adjustments are possible, new high-grade incompetence may suggest inaccurate septation and partitioning of the AV valves, which could require more extensive revision, as discussed above. AV valve replacement in an infant introduces a host of secondary problems. It is rarely necessary, and should be avoided except in dire situations. Discrepancies between intraoperative transesophageal echo studies and postoperative transthoracic studies have been noted in various studies, and in general, useful intraoperative interpretation for the surgical team requires an interested and experienced echocardiographer [17]. Irrespective of echo-assessed competence, which can be elusive to quantitate, the key point is the ability of the patient to remain well following extubation, which in itself would be suggestive of acceptable AV valve function.

Left ventricular outflow tract obstruction (LVOTO) is a theoretical problem in any type AVSD repair, and more so when complicated by tetralogy of Fallot. This is attributable to the non-wedged position of the aorta and "gooseneck" anatomy of the LVOTO in AVSD, which might be exacerbated by approximating AVV tissue to the septal crest. In fact, this has not been a problem in clinical practice with the Nunn repair, with the incidence of minor LV-Aorta gradients being similar to that experienced with other techniques (see below) [8].

Outcome of Surgery

Analysis of recent results in the ECHSA Congenital Database from 2008 to 2018 (currently with 392 centers from 83 countries contributing), reveals a number of trends regarding repair



2-patch repair	115	98	87	80	77	68	52	40	25	13	2	0
Nunn repair	41	38	30	14	3	0	0	0	0	0	0	0

Number at risk

Fig. 105.14 Freedom from re-intervention due to either atrioventricular (AVV) dysfunction or left ventricular outflow tract obstruction (LVOTO) following atrioventricular septal defect repair. Cox regression did not reveal a statistically significant difference in the risk of re-intervention in either group. The hazard ratio (Nunn repair group) was 0.512 (95% CI: 0.176–1.49). (Bell D et al. Propensity matched comparison of the long-term outcomes of modified single-patch (Nunn) and two-patch techniques for repair of complete atrioventricular septal defects. (2018, Article in press))

of complete AVSD. Considering all patients operated in the first year of life (using any technique) (n = 4088), hospital mortality was 4.33%. Three "gold standard" centers reported 0% mortality (n = 164). Hospital mortality for infants with trisomy 21 within the entire group was 2.39%. For the neonates (n = 39) within the entire group, hospital mortality was 10.26%. For patients operated between 1 and 12 months of age (n = 4049), hospital mortality was 3.31%, with three "gold standard" hospitals reporting 0% mortality (n = 175).

Multi-institutional results from Sydney and Brisbane were presented in 2014, with a hospital mortality of 1.3% (n = 150). Over a mean follow-up time of 7.1 years, there were five re-operations, all for left AV valve insufficiency. LVOTO observed in this series was generally mild, and no re-operations for that problem were required. Longer term follow-up may be needed to fully assess the issue [8, 18, 19].

More recently, Li and colleagues analyzed 15 publications involving 1034 patients undergoing repair of AVSD. The VSD size was significantly smaller in patients undergoing the Nunn repair, as compared to patients operated by other techniques. The Nunn repair group also had shorter ischemic and CPB times and length of stay compared to a two-patch repair cohort. They found no differences between the two groups in hospital mortality, incidence of LVOT obstruction, residual VSD, complete heart block, or need for reoperation [20].

In a 2018 analysis from Brisbane, a retrospective but propensity matched comparison of the outcome of the Nunn and classical two-patch techniques for multiple surgeons (1998–2015) was performed [21]. Mortality (4.5%) was similar in the two groups (n = 156, $p = 0.75$). Duration of both CPB and cardioplegic arrest was longer for the two-patch group ($p < 0.001$ for each). Cox regression analysis of the propensity matched sample (37 pairs) demonstrated no difference in freedom from re-operation between the two techniques (Fig. 105.14). The proportion of patients with moderate or worse left AVV regurgitation was higher for the two-patch group (29%) compared with 10% in the Nunn repair group. There was no statistically significant difference in the incidence of echo-detectable LVOTO (7.2%) between groups ($p = 0.339$).

There is no question that there is a learning curve for repair of AVSD [22]. Evidence is accumulating, however, that the Nunn technique is an effective option for repair of AVSD across the age and morphology spectrum [8, 18, 19, 23–25]. The most consistent finding is not necessarily lower mortality (which has already been achieved with other techniques), but rather a simpler, faster, and more reproducible operative experience, with favorable preservation of AV valve function.

Conclusion

The Nunn technique is an expedient and useful strategy that may ultimately compare favorably to previous repair techniques. The limits of its applicability are yet to be determined, especially in patients with very large VSDs, or tetralogy of Fallot. It is, however, a good option for the majority of patients, with equipoise in comparison to other techniques. As is often the case in pediatric cardiac surgery, a prospective RCT would be difficult to conduct at this point.

The repair of complete AVSD in infancy effectively alters the natural history, although the disease and its treatment still carry a significant risk, especially in neonates.

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Double Outlet Right Ventricle

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Ravi S. Samraj, Ross M. Ungerleider, and Inder Mehta

High Yield Facts

- Double outlet right ventricle (DORV) is a rare congenital heart disorder with a reported incidence of about 3–9/100,000 live births.
- DORV is defined as the condition in which both the pulmonary artery and aorta arise from the morphologic RV.
- Chromosomal abnormalities have been reported in 41% of the patients with DORV.
- The key components of DORV anatomy include the relation of VSD to the great arteries and the presence or absence of outflow tract obstruction. These two critical elements dictate the pulmonary systemic perfusion balance (Q_P:Q_S) as well as the surgical options.
- Surgical options include one-stage biventricular repair, biventricular repair with a conduit, or staged palliative single-ventricle surgery.
- Overall hospital mortality of 6–9% has been reported in published studies in the current era.
- Recent large studies have reported a 15 year overall survival between 56% and 90%.
- Patients after DORV surgery need reintervention sometime in the future. Reported rates of first reintervention are 19% at 5 years, 31% after 10 years and 41% after 15 years post complete repair.

Introduction

Double outlet right ventricle (DORV) is a unique cardiac pathology which displays a wide spectrum of pathoanatomic variations. It occurs in 1–3% of individuals with congenital heart defects [1] with a reported incidence is about 3–9/100,000 live births [2, 3]. An in-depth understanding of this pathology and its variations is critical in providing optimal perioperative care and in formulating the appropriate surgical intervention.

Historical Perspective

The first pathologic description of DORV was in early eighteenth century by Abernethy who commented that "both ventricles, the left by means of an opening in the upper part of the septum ventriculorum, projected their blood into the aorta" [4]. However, Vierordt in late nineteenth century considered it as a partial transposition of great arteries (TGA) since only the aorta had a discordant relationship with the ventricle while the pulmonary artery (PA) did not exhibit such discordance [5]. Witham first used the term DORV in 1957 [6] while the surgical repair for DORV was first published by McGoon in 1961 [7].

Definition

DORV is defined as the condition in which both the pulmonary artery and aorta arise from the morphologic RV. Aorta is defined as arising from the RV when it overrides the septal crest by more than 50% and thus is predominantly associated with the RV. A ventricular septal defect (VSD) is present in most cases (but not always) and serves as an outlet to the left ventricle (LV). Due to the variable position of the great arteries and their relationship with VSD, it may be difficult to differentiate the lesion from tetralogy of Fallot (TOF) or transposition of great arteries (TGA). In these cases, a complete lack of fibrous continuity between semilunar valve and the mitral valve and overriding of the great arteries by more than 50%

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relating to the RV helps in differentiating DORV from TOF and d-TGA respectively. Although the presence of aortic-mitral discontinuity and bilateral coni are important descriptors, they should not serve as absolute prerequisites for the diagnosis of DORV [8]. These defining criteria may overlap with other cardiac phenotypes resulting in confusion. The 50% rule becomes problematic in cases of tetralogy of Fallot with extreme override of aorta. Similarly, absence or loss of normal fibrous continuity between mitral and aortic valves and persistence of subaortic conus is variable in DORV [1, 8]. The Congenital Heart Surgery Nomenclature and Database Project gave consensus broad definition by stating "DORV is a type of ventriculoarterial connection in which both great vessels arise either entirely or predominantly from the right ventricle" [8].

Embryology

Early embryonic development is characterized by the presence of a single outflow tract from the distal part of the ventricular loop of the developing heart. This single outflow tract arises exclusively from the right ventricle. The most proximal part of the outflow tract is separated by the fusion of the cushions within it to produce the subpulmonary infundibulum, while the subaortic part of the outflow tract is partitioned to the left ventricle by the fusion of the cushions to the crest of ventricular septum [9]. Following the looping of the ventricles, the subaortic conus normally absorbs so that the aortic valve descends to an inferior posterior location. However failure of this process and persistence of the subaortic conus leaves the aorta rightward and ventral resulting in the aorta being associated with the RV [10]. Other researchers have shown that DORV can also result from abnormal development of the AV endocardial cushions [10].

Genetics

No single underlying genetic or chromosomal disorder for DORV has been identified. However chromosomal abnormalities have been reported in 41% of the patients [8]. Associations reported include trisomy 12, trisomy 18, trisomy 21 and CATCH 22 syndrome [8, 11, 12]. Most common mutations associated with DORV include CFC1, CSX, Hand2, PITX2 and ZIC3 gene mutations in humans. Animal studies implicate maternal diabetes, prenatal exposure to ethanol, retinoids, theophylline and valproate in DORV teratogenesis [8].

Morphology

The key components of DORV anatomy include the relation of VSD to the great arteries and the presence or absence of outflow tract obstruction. These two critical elements dictate the pulmonary systemic perfusion balance (Q_P:Q_S) as well as the surgical options. The other aspects of anatomy to pay attention to include the atrial arrangement, atrioventricular connections, atrioventricular valve morphology, ventriculo-arterial connection, relationships of arterial trunks and associated defects. In a study of 84 specimens of DORV with usual atrial arrangement and concordant AV connections by Wilkinson et al., the six most common associated defects included pulmonary stenosis (37%), atrial septal defect (23%), coarctation (19%), mitral stenosis (8%), straddling mitral valve (7%) and hypoplastic left ventricle (6%) [13].

Ventricular Septal Defect

A VSD is almost always present. Rarely when it is absent, the blood from the LV uses an insufficient mitral valve and an ASD as an outlet to the right heart. Lev et al., in 1972 used the relationship of VSD to the great arteries as the basis for his classification [14]. Four types of VSD were described, this is dictated by the variable position of the conal septum in relation to the VSD rather than changes in the VSD location [8].

Subaortic VSD

This is the commonest type of VSD in patients with DORV, occurring in 42–59% of patients. VSDs are usually perimembranous. This is the usual type seen when DORV is associated with L-malposition of the aorta. The conal septum is deviated anteriorly and leftward leading to streaming of the LV blood preferentially into the aorta. Physiology is similar to isolated VSD physiology. Pulmonary outflow tract obstruction is associated in most of the patients due to crowding of the subpulmonary area by the conal deviation.

Subpulmonic VSD

This is the second most common type occurring in 21–37% if the patients. Majority of these patients have no pulmonary stenosis. Physiology resembles that of d-TGA. A variation of this anatomy results in Taussig Bing anomaly (DORV, subpulmonic VSD, side by side great vessels, bilateral conus and not uncommonly subaortic stenosis due to hypertrophy of the infundibular septum and the parietal band) [15].

Non-committed VSD

In this type, the VSD is remote from the aortic and pulmonary valves [16]. Occurs less commonly, in 10–20% of patients. This type is usually seen when DORV is associated with complete atrioventricular septal defect. Pulmonary stenosis is uncommon in patients with non-committed VSD.

Doubly Committed VSD

This is the most uncommon type, occurs in 3–9% of patients. In this variant, the infundibular septum is absent leaving both aortic and pulmonary valves related to the VSD. Clinical features are dictated by the presence or absence of pulmonary stenosis.

DORV Classification

The Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery Nomenclature and Database Project proposed a current and widely accepted classification system for DORV based on the clinical presentation and treatment strategy [8].

1. TOF type: DORV with pulmonary stenosis, most common type with a prevalence of 35%.
2. VSD type: DORV with a subaortic VSD, occurs in 25% of patients.
3. TGA type: DORV wherein the pulmonary artery is closely associated with the left ventricle, with a prevalence of 20%
4. Non-committed VSD type: DORV where the ventricular septal defect is remote from the semilunar valves, with a prevalence of 20%. The VSD is usually a muscular or inlet defect, and the distance from the aorta and pulmonary artery is at least 1 aortic diameter [17].

Associated Anomalies [1, 5, 18]

Intracardiac	Extracardiac
Pulmonary stenosis	Heterotaxy syndromes (16%)
Subaortic stenosis	Urogenital malformations (9%)
Aortic valvular stenosis, coarctation, interrupted aorta	Congenital diaphragmatic hernia (6%)
Mitral valve anomalies: stenosis, atresia, cleft, double orifice, straddling valve	Trisomy 13, Trisomy 18, Trisomy 21, chromosomal del 22q11
Ebstein's malformation of the tricuspid valve	
Common atrioventricular canal	
Hypoplastic RV or LV	
Juxta position of the atrial appendages	
Abnormal coronary artery patterns (50%)	

Pathophysiology

Given the wide variety of anatomic pathologies of DORV, the pathophysiology can vary from patient to patient significantly based on several factors. Similar to other mixing congenital heart lesions, the clinical course is dictated by the amount of pulmonary blood flow and systemic blood flow. Several factors are important in determining the physiology and clinical presentation: location and size of VSD, great artery relation to each other, associated defects (pulmonary or systemic outlet obstruction, patent ductus arteriosus) and pulmonary vascular resistance.

Ventricular Septal Defect and Great Artery Relation

An unrestrictive VSD equalizes the RV and LV pressures, consequently the pulmonary (Qp) and the systemic blood flow (Qs) is determined by the outflow obstruction and factors downstream like pulmonary vascular resistance and systemic vascular resistance. The commitment of the VSD determines streaming. For example, in TGA type DORV hypoxia results from inadequate mixing of the ventricular blood and streaming of the blood from RV directly into aorta. This is less of a problem in single ventricle variants where there is complete mixing before the ventricle empties the blood into the great vessels. When the VSD is subaortic in location without any significant pulmonary stenosis, there is minimal mixing and the LV blood is ejected directly into the aorta resulting in high aortic oxygen saturations. This physiology is similar to that of an isolated VSD with concordant ventriculo-arterial connections. In these patients the Qp:Qs is determined by the pulmonary vascular resistance. A variant of DORV, Taussig-Bing malformation (DORV, subpulmonary VSD, side by side great arteries, bilateral conus) has a physiology similar to TGA resulting in lower saturation in aorta and higher saturation in the pulmonary artery. A non-committed remote VSD has a physiology similar to that of an isolated VSD or atrioventricular canal defect. The Qp:Qs in this case is determined by the ratio of pulmonary to systemic vascular resistance, similar to patients with DORV and doubly committed VSD.

Patent Ductus Arteriosus

Patients can have a patent ductus arteriosus (PDA) dependent pulmonary circulation (pulmonary atresia, severe pulmonary stenosis) or PDA dependent systemic circulation (arch obstruction, aortic stenosis) making it necessary for sustaining life. On the other hand, PDA can result in pulmonary over circulation in some patients and worsen heart failure and/or respiratory failure. Patients with left ventricular outflow tract obstruction (aortic stenosis, arch obstruction) result in systemic hypoperfusion once the PDA closes.

Pulmonary Vascular Resistance

In the first few weeks of life, pulmonary vascular resistance (PVR) is high and prevents pulmonary over circulation.

After this period, the PVR drops below systemic vascular resistance (SVR) resulting in increasing Qp:Qs in the absence of other modifying factors. Uncorrected lesions for prolonged periods result in increased flow and PVR, leading to progressive cyanosis.

Clinical Presentation

Patients with DORV can present in congestive heart failure or in respiratory failure secondary to pulmonary over circulation. Most of them present within the first few days to weeks of life. However patients with balanced physiology may remain asymptomatic for a longer time. Clinical features are dependent on the anatomic type of DORV, can be extremely variable and may mimic presentation of several other congenital heart lesions. The timing and severity of symptoms is also affected by the normal decrease in PVR that happens after birth as well as the presence or absence of PDA and degree of outflow tract obstruction.

In the absence of significant pulmonary stenosis, DORV with VSDs located anywhere but the subpulmonic region are indistinguishable from large VSDs in presentation. Patients without pulmonary stenosis usually present with some degree of heart failure and with recurrent pulmonary infections. Pulmonary stenosis limits pulmonary blood flow and, depending upon its severity, can produce various degree of cyanosis. In the TOF type, severity and timing of presentation depends on the degree of pulmonary stenosis (PS). Patients with mild PS may initially be asymptomatic and present later while patients with severe PS present initially with cyanosis. In this type, the cyanosis increases with time and patients may have hyper cyanotic spells similar to TOF patients due to dynamic subpulmonary obstruction. In the VSD type DORV patients associated with subaortic VSD, cyanosis can be present early and the degree of cyanosis is related to the severity of PS. In the absence of PS in these patients, they present later in life with congestive heart failure and failure to thrive similar to a patient with isolated VSD. In the TGA type DORV with subpulmonary VSD, patients exhibit early cyanosis due to inadequate mixing and RV to aortic blood streaming as mentioned earlier.

Physical Signs

Cyanosis may be present at birth in patients with severe lesions or may not manifest till later in patients with milder lesions and well balanced circulations. Patients may show signs of congestive heart failure (irritability, vomiting, poor perfusion, tachycardia, feed intolerance, poor urine output) or pulmonary over circulation (respiratory distress, poor feeding, tachypnea, cyanosis). Auscultatory findings may vary based on the underlying pathology. An ejection systolic murmur of varying severity may be audible along the left upper sternal border related to the infundibular or pulmonic stenosis. Second sound may be single due to absence of the pulmonic component, especially in the TOF type. A harsh parasternal murmur may reflect the underlying VSD while an apical mid-diastolic murmur may indicate high flow or associated mitral stenosis. A forceful apical impulse may be seen due to left ventricular hypertrophy. In patients with associated aortic arch anomalies, femoral pulses may be diminished.

Diagnosis

Diagnosis is made prenatally in most instances with fetal ultrasonography. Initial diagnostic tests include a chest radiograph, electrocardiogram and echocardiogram. Chest radiograph helps to evaluate for pulmonary oligemia, pulmonary plethora, and cardiomegaly. Electrocardiogram is nonspecific and may show prolonged PR interval and signs of atrial or ventricular hypertrophy. Left ventricular hypertrophy can be seen either due to pressure overload (restrictive septum) or volume overload (increased pulmonary venous return). A detailed echocardiogram should be done to delineate the anatomy with particular attention to segmental situs, degree of commitment of both great arteries to the right ventricle, spatial relation of both great arteries, adequacy of ventricular size, size/location/number of VSD, presence of pulmonary or systemic outflow tract obstruction, associated cardiac anomalies, coronary artery anatomy, presence of restrictive septum, absence or loss of normal fibrous continuity between mitral and aortic valves and persistence of subaortic conus. Occasionally, cardiac catheterization and angiography might have to be obtained when the echocardiogram is insufficient to provide all the relevant details. Catheterization helps to study the hemodynamics and evaluate the ventricular volumes, PVR, VSD gradient, relationship of VSD and great arteries, degree of shunting, Qp:Qs, coronary anatomy and aortic arch anatomy. Catheterization may also be necessary to perform an atrial septostomy in patients with a restrictive septum. Cardiac MRI can also help delineate the anatomy in selected cases in whom echocardiography provides insufficient data.

Management

Preoperative Management

Prior to surgery, management consists of stabilization of the hemodynamic status, evaluation of the cardiac anatomy and preparation for definitive surgical management. After birth, patient should be adequately resuscitated and appropriate vascular access obtained. Prostaglandin E1 therapy to maintain ductal patency is initiated while awaiting the confirmation of diagnosis and till definitive therapy if required (ductal dependent pulmonary or systemic circulation). Congestive heart failure is managed with optimal use of diuretics and afterload reducing agents if necessary. Care should be taken to minimize the use of oxygen as it is a potent pulmonary vasodilator and can exacerbate pulmonary edema. Systemic oxygen saturations between 75% and 85% is adequate while awaiting definitive treatment. These levels maintain adequate oxygenation while avoiding pulmonary overcirculation at the same time. Careful attention should be paid to the adequacy of systemic tissue perfusion and it is a common practice to tolerate higher systemic oxygen saturations if it is not impairing systemic tissue perfusion or causing respiratory failure from pulmonary over circulation. Patients with restrictive septum may need an emergent atrial septostomy to promote mixing and improving cardiac output while awaiting definitive repair.

Postoperative Management

Patients with DORV are at risk of significant postoperative problems and need meticulous monitoring for early detection and prompt intervention. Monitoring the heart rate, rhythm, arterial blood pressure, central venous pressure, atrial pressures (if intracardiac lines were placed), regional oxygen saturation (cerebral, renal), urine output, peripheral perfusion, central venous oxygen saturation ($ScVO_2$) and serum lactate levels help to assess the hemodynamic status and cardiac output in the postoperative period. Complications in the immediate postoperative period include low cardiac output syndrome (LCOS), cardiac arrhythmias, pulmonary hypertension, residual lesions and postoperative bleeding.

1. *Low cardiac output syndrome*: LCOS is not uncommon after surgical repair and can be due to multiple factors including systemic inflammatory response to cardiopulmonary bypass, myocardial edema, ventriculotomy, impaired myocardial function, arrhythmias, pulmonary hypertension, coronary problems, fixed obstruction and residual lesions [19]. Postoperative transesophageal echocardiogram is done in all patients in the operating room and gives an estimate of the cardiac function and presence of residual lesions. Low cardiac output after surgery should be managed with judicious balance of inotropy, adequate preload and afterload reduction. Routine use of inotropes after surgery has reduced the incidence of LCOS. Milrinone in particular helps by improving the myocardial contractility as well as by achieving afterload reduction. Low dose epinephrine may also help in achieving afterload reduction. Careful attention should be paid to dose and duration of fluid boluses as they can lead to significant increase in ventricular wall stress causing decreased coronary perfusion, and pulmonary edema leading to RV failure. Delayed sternal closure may help to avoid high intrathoracic pressures which can decrease cardiac output by impeding the venous return to the heart. Mechanical circulatory support and redo surgery may be necessary in some patients unresponsive to medical management.
2. *Cardiac arrhythmias*: Complete heart block (CHB) and junctional ectopic tachycardia (JET) are the two most common arrhythmias occurring after surgery. VSD closure or manipulation during the surgery places the patients at risk for CHB. Pacing wires are routinely placed after surgery to facilitate external cardiac pacing if necessary in the postoperative period. The heart block usually recovers in the first few days. However persistence for 7–10 days after the surgery may require placement of a permanent pacemaker. JET usually occurs in the early postoperative period. This is more common in patients who require muscle resection of the outflow tract. Treatment includes avoidance of hyperthermia, decreased use of sympathomimetics, judicious use of sedatives, use of dexmedetomidine, external cooling and temporary cardiac pacing.
3. *Pulmonary hypertension*: This can result from pre-existing pulmonary vasoreactivity, cardiopulmonary bypass related inflammatory cytokines, acidosis, and hypoxia. A significant increase in the RV afterload can occur during these episodes of pulmonary hypertension and can lead to low cardiac output, bradycardia and cardiac arrest. Therapeutic options include adequate sedation, avoidance of acidosis/hypoxia/agitation, hyperventilation, inhaled nitric oxide for pulmonary vasodilation and judicious use of paralysis. In patients at high risk of pulmonary hypertension, a patent foramen ovale is left open during surgery to avoid acute RV dilation and to ensure continued LV filling and cardiac output.
4. *Residual lesions*: Although transesophageal echocardiogram in the operating room evaluates for residual lesions, it is important to have a low threshold to reevaluate for these lesions in the postoperative period when dealing with a hemodynamically unstable patient. Two common residual lesions in this patient population include residual VSD and aortic insufficiency. Patients with residual VSD may need reoperation particularly if the Qp:Qs is more than 2 or if unable to be weaned from the ventilator. Aortic insufficiency can result from conal septal separation near the valve or from sutures placed for a VSD near the valve. Other lesions that can lead to low cardiac output include tricuspid insufficiency, right ventricular out-

flow tract obstruction (after repair of DORV with severe PS) and systemic outflow tract obstruction (after intracardiac baffle repair or after arterial switch of DORV with subpulmonic VSD).

5. *Postoperative bleeding*: Significant postoperative bleeding can result in hemorrhagic shock, severe anemia and cardiac tamponade. All of these impair cardiac function. Routine use of antifibrinolytic therapy (tranexamic acid, aminocaproic acid) can help reduce the amount of postoperative bleeding. Treatment includes replacing blood products, volume resuscitation, drainage of pericardial collection and surgical exploration if necessary.

Surgical Management

The fact that these lesions can be complex is demonstrated by the study by Wilcox et al. [20]. Among 63 hearts with DORV, it was determined that 23 (36.5%) were inoperable for a two ventricle repair, as a result of their anatomic aberrancy. This group of hearts had associated lesions such as straddling valves, multiple septal defects, left ventricular hypoplasia, or other combinations of complex lesions that made the possibility of successful two ventricle repair unlikely. In an autopsy series of 50 hearts with DORV [21], 26 were found to be so severely abnormal that surgical correction could not have been performed. Despite these discouraging figures, DORV is often a correctable lesion with an increasingly improving surgical outlook.

To plan suitable surgical repair, the surgeon must know the orientation of the great vessels, the location (and size) of the VSD and its relationship to the great arteries, the distribution and location of the coronary arteries, whether there is pulmonic or aortic stenosis, and the nature of any associated intra- or extracardiac anomalies [20]. These data must be combined with information regarding hemodynamics obtained from echocardiographic examination and cardiac catheterization [22]. The goal of operation is to separate the systemic and pulmonary circulations. This can be accomplished by the use of intraventricular tunnels or extracardiac conduits. These types of repair require the use of cardiopulmonary bypass (CPB). In infants, deep hypothermia with total circulatory arrest may be desirable, but the procedure can also be performed with moderate hypothermia and cardioplegia. Palliation in infancy (i.e., placement of systemic-pulmonary artery shunt) may be appropriate in those patients requiring an extracardiac conduit as part of the eventual repair. This permits achievement of a size that will allow placement of a larger conduit.

The most common form of DORV is that associated with a subaortic VSD with or without pulmonary stenosis. Repair of this lesion proceeds in a manner similar to that for repair of tetralogy of Fallot. Repair can be performed in infancy if the caliber of the pulmonary arteries is acceptable. After the patient is placed on CPB, the right ventricle is opened in a region that avoids the coronary arteries. The orifices of both great arteries are identified and areas of subpulmonic, infundibular stenosis are relieved. Because the infundibular septum, which separates the aortic and pulmonary valves, can be oriented in a more sagittal plane than normal (depending on the orientation of the great vessels), care must be taken to avoid incising this area and damaging the aortic valve. The VSD is identified and its borders clearly visualized. If the VSD is smaller than the orifice of the aortic valve, it can usually be safely enlarged in an anterior and superior direction [23, 24]. Once again, caution is necessary when enlarging the VSD so that enough border is maintained to allow secure placement of sutures for the intracardiac baffle. In most cases of subaortic and doubly committed VSDs, a patch can usually be fashioned that directs left ventricular outflow into the aorta while avoiding the orifice to the pulmonary artery. Reconstruction of the right ventricular outflow tract is then accomplished to complete the repair. This can usually be performed during rewarming so that CPB time is reduced. RV outflow can be augmented in several ways, including simple closure of the ventriculotomy, RV outflow patching (with pericardium or prosthetic material), which can extend across the pulmonary valve annulus if necessary to relieve pulmonary valvar stenosis, or even with the uses of a valved external conduit (as might be necessary in the case of sever pulmonary stenosis that is not amenable to transannular patching because of an anomalous coronary artery). In addition, patients with pulmonary hypertension requiring transannular patching may do better with a valved conduit—preferably homograft—to protect the right ventricle [25]. Complications of this type of repair include obstruction to LV outflow from a poorly configured patch [26], hemolysis across the patch (which usually disappears within 6 weeks after the surface of the baffle endothelializes) [27], heart block and other arrhythmias, bleeding, and heart failure (usually right ventricular if there is substantial pulmonary hypertension). In patients with significant pulmonary hypertension, repair can be accomplished through the right atrium [25, 26, 28]. Because of the potential for dysrhythmias, it is recommended that temporary atrial and ventricular pacing wires be left prior to closure of the chest. When DORV is associated with a noncommitted VSD, repair follows the same principles but is usually more difficult because the length and configuration of the patch may increase the risk of subaortic, baffle obstruction to LV outflow. This problem can be diminished, in part, by generous enlargement of the VSD away from the conduction tissue. When the patient has an associated complete AV canal defect, repair of the entire lesion can usually be performed, but once again, careful attention must be given to the intraventricular baffle with anterior-superior enlargement of the inlet type

VSD if necessary. DORV can also commonly occur in association with abnormalities of the aortic arch (i.e., coarctation). It is usually preferable to repair the arch anomaly at the time of DORV repair and this can be achieved easily through a median sternotomy [29].

The surgical repair of DORV with subpulmonary VSD has evolved through several modifications. Although placement of an intracardiac baffle to direct LV outflow toward the aorta remained a favorable option, the location of the VSD in proximity to the pulmonary orifice and the presence of the frequently present muscle bands from the infundibular septum could make construction of this baffle technically demanding or even impractical. Nevertheless, careful resection of muscle and placement of the suture line may allow this type of repair in selected patients [30]. It is usually advisable to inspect the anatomical features through the right atriotomy to ascertain the potential for this type of repair prior to performing a right ventriculotomy. If the patient proves to have findings incompatible with an intracardiac baffle, it may be possible to close the VSD through the right atrium in a manner that directs LV outflow into the pulmonary artery. The patient can then be treated as one with TGA, and an arterial switch can be performed. Arterial switch procedure has a good success rate [31], and is the preferred surgery for these patients [32]. If this operation is chosen, it can be performed in infancy, although not with the same urgency as with simple TGA, since the VSD can be depended on to maintain left ventricular pressures until the actual time of operation (as in TGA with large VSD). However, when an arterial switch is chosen then the VSD can be repaired though the atrium, the proximal pulmonary artery (neo aorta; although it is important to keep the sutures on the RV side of the inferior part of the septum to avoid creation of heart block), or through a right ventriculotomy [24]. If the VSD is closed through a right ventriculotomy, this can be done during rewarming after the coronary transfer has been completed.

There are instances in which the arterial switch may not be appropriate. The presence of significant subaortic stenosis might contraindicate the performance of arterial switch, depending upon the feasibility of opening the right ventricular outflow into the aorta (new-pulmonary artery). In these patients, arterial switch without coronary translocation (Damus-Kaye-Stansel procedure) can be performed [25]. This requires patching of the VSD into the pulmonary artery, and diversion of the proximal pulmonary artery end-to-side into the aorta. RV to PA continuity is restored with the use of an external conduit. If severe subpulmonic stenosis is present, then arterial switch is contraindicated and the lesion should be repaired using the Rastelli procedure. In this operation, the VSD is baffled to be the aorta (through a right ventriculotomy) and the pulmonary artery is divided. The proximal pulmonary artery is oversewn, and RV to PA continuity is established with the use of an external conduit. Because symptomatic infants with DORV and subpulmonary VSDs usually require a combination of banding and shunting [33], (if palliation is chosen), our preference is to attempt early total repair, preferably with arterial switch, but with the recognition that external conduits can be safely applied to the infant population [34]. The ready availability and excellent performance of allografts further favor this approach [35, 36]. In patients with severe atrioventricular valve abnormalities (i.e., straddling chordae) or other complicated pictures, it may be necessary to stage the patient towards a modified Fontan procedure [26].

Outcomes

Prior to the “current era,” the overall risk of hospital mortality for repair of DORV (all forms) ranged from 11% to 40% and was largely influenced by the type of DORV (patients with subaortic and doubly committed VSDs having a better prognosis than those with subpulmonary VSDs), as well as by age at operation (young age being a risk factor), type of operation performed (intraventricular tunnel repairs leading to better results than atrial switch and external conduit procedures), and the presence of severe associated cardiac anomalies or significant pulmonary hypertension [37–40]. Because of the high risk of early repair, it was considered reasonable to palliate patients: with systemic to pulmonary artery shunts (if pulmonary stenosis was present), with pulmonary artery bands (if there was no pulmonary stenosis), and with a combination of the two (for patients with subpulmonary VSDs who presented with cyanosis in the face of high pulmonary blood flow) [33]. Despite these protocols, the long-term survival for patients with DORV remained a dismal 38% at 12 years (and is as low as 22% over 10 years for patients with noncommitted VSDs) [41]. Previous studies have shown that late mortality was influenced by conduit stenosis, late dysrhythmias, and heart failure—often due to progressive pulmonary hypertension [23, 26, 40, 41].

However, improvements in surgical techniques and postoperative care have significantly improved outcomes for all congenital heart surgeries in general and for DORV in particular. Immediate postoperative outcomes are excellent in the current era. Overall hospital mortality of 6–9% has been reported in published studies [42, 43]. Long term outcomes have also improved compared to previous era. Recent large studies have reported a 15 year overall survival between 56% and 90% [44–46]. In a retrospective study of 393 children with DORV treated at a single institution between 1980 and 2000, 10.4% did not have any intervention, 19.3% underwent palliation only, 20.9% underwent a single ventricle repair while 49.4% underwent a double ventricular repair [44]. Outcomes in this study were best for patients who underwent a biventricular repair (10 year survival 86%) compared to patients who underwent a single ventricle repair, as well as for patients who were treated in the second half of the study period. Similar improvement in hospital mortality over different time periods has been reported in other studies (41% before 1980 vs. 13% thereafter) [46].

Patients after DORV surgery need reintervention sometime in the future. Reported rates of first reintervention are 19% at 5 years, 31% after 10 years and 41% after 15 years post complete repair [44]. The most common reinterventions after single ventricle repairs included fenestration closure, coil-occlusion of collaterals, valve repair/replacement, pacemaker insertion, pulmonary artery dilation/arterioplasty, Fontan revision, repair of aortic coarctation and myomectomy for subaortic stenosis. Interventions after biventricular repairs included relief of RVOT obstruction, relief of LVOT obstruction, pulmonary artery dilation/arterioplasty, RVOT aneurysm repair, valve repair/replacement, residual VSD closure and pacemaker implantation [44]. Patients requiring a right ventricle to pulmonary artery conduit will invariably need conduit replacement sometime after surgery depending on conduit type [47]. Risk of subaortic stenosis is particularly high after intraventricular repair of DORV with subpulmonary VSD [44]. Neo aortic valve incompetence is common in DORV patients who undergo an arterial switch for transposition physiology [48]. Other long term complications include arrhythmias, endocarditis, thromboembolic phenomena, sudden death, poor nutritional status and psychiatric co-morbidities.

Overall, the results for most forms of DORV include a low operative mortality with excellent long-term survival and quality of life. Surgical repair early in life helps to avoid the risk of irreversible pulmonary hypertension and reduces the complications of multiple operative procedures associated with initial palliation.

Conclusion

DORV is a constellation of anatomically related complex congenital heart lesions involving the right ventricular outflow tract. There are a number of variations within the diagnostic category of DORV that give rise to a wide spectrum of physiology ranging from that of tetralogy of Fallot to TGA to true single ventricle physiology. It therefore encompasses virtually the entire spectrum of cardiac physiology. Understanding of the specific relationship of the VSD to the great vessels, the size of the VSD, the size of the great vessels, the ventricular size, and the status of the AV valves is crucial to predict the physiology and the most appropriate treatment. Repair may consist of one-stage biventricular repair, biventricular repair with a conduit, or staged palliative single-ventricle surgery. Surgical treatment can be offered to most patients with low operative mortality and good mid- to long-term outcome.

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Neonatal Ebstein's Anomaly

Umar S. Boston, Ken Bayle, T. K. Susheel Kumar,
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High Yield Facts

- Ebstein's anomaly is a rare congenital heart defect with a prevalence of 2.4 per 10,000 live births.
- Neonatal Ebstein's anomaly is associated with high mortality ranging from 17% to 56%.
- The Great Ormond Street Echocardiogram (G.O.S.E.) score is a mortality risk stratification score for neonates with Ebstein's anomaly.
- Medical management through the neonatal period is associated with better surgical outcomes.
- Surgical approaches for the management of these critically ill neonates have varied across institutions and include the Starnes right ventricle exclusion procedure, systemic–pulmonary shunts, hybrid-type procedures, biventricular repair and heart transplantation.
- Biventricular repair is feasible with good long-term outcomes.
- Monocusp repair utilizing the anterior leaflet is a reproducible and durable tricuspid vavluloplasty technique.

Introduction

Described by Wilhelm Ebstein in 1866 [1], Ebstein's anomaly (EA) is a rare congenital heart defect with a prevalence of 2.4 per 10,000 live births [2]. EA is a result of varying degrees of failure of the leaflets of the tricuspid valve (TV) to delaminate from the underlying endocardium. Importantly, the right ventricle (RV) in EA is myopathic which has significant importance for the symptomatic neonate.

The clinical presentation relates to a combination of the degree of tricuspid valve regurgitation and the degree of right ventricular dysfunction. Furthermore, there is a bimodal distribution of the clinical manifestations of EA; those who present in adulthood and those in the neonatal period. In utero and neonatal presentation is associated with high mortality. An in utero diagnosis of EA has an incidence of 48% fetal demise, often related to hydrops and arrhythmia [3]. Mortality for EA in the neonatal period ranges from 17% to 56% [4], posing significant medical and surgical challenges.

Associated Anomalies and Arrhythmias

There are a number of concomitant cardiac defects which have important clinical relevance in neonatal EA. A patent foramen ovale or atrial septal defect (ASD) is normally present. Tricuspid regurgitation or right ventricular dysfunction leads to right to left shunting across the defect accounting for cyanosis. Anatomical pulmonary atresia is present in 50% of symptomatic neonates undergoing surgical intervention [5]. Functional pulmonary atresia can also be present when the pulmonary vascular resistance (PVR) is high and the right ventricle is dysfunctional and cannot generate antegrade flow across the pulmonary valve. Anatomical and functional pulmonary atresia, results in ductal dependency and the requirement for prostaglandins.

Other associated cardiac defects include ventricular septal defect, atrioventricular canal defect, tetralogy of Fallot and corrected transposition of the great arteries [6–8]. Myopathy of the left ventricle (LV) has also been associated with EA. Left ventricular non-compaction is present in 16% of patients with EA and is a risk factor for mortality [7].

EA can be associated with many forms of atrial level arrhythmias. Wolff-Parkinson-White (WPW) has an incidence of 10–30% of EA patients [9, 10]. Due to large right

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atrium, EA patients are at risk for atrial tachycardia, atrial flutter, intra-atrial reentrant tachycardia, atrial fibrillation, AV note reentrant tachycardia, and ventricular arrhythmias.

Anatomy of Ebstein's Anomaly

1. Embryological failure of delamination of the TV leads to tethered leaflets to the endocardium by fibromuscular attachments or abnormal foreshortened chordae. Each leaflet exhibits varying degrees of apical displacement and tethering with the septal leaflet most severely affected followed by posterior then anterior leaflets. This results in anterior and apical displacement of the functional annulus.
2. The anterior leaflet is attached to the true anatomical annulus but is large or sail like.
3. The portion of the RV above the functional annulus ('atrialized right ventricle') is dilated and thin. The true tricuspid annulus is almost always enlarged. In a neonate this measures approximately 21 mm.
4. The cavity of the effective RV is reduced ('functional right ventricle').
5. The infundibulum of the RV can be obstructed by the redundant tissue of the anterior leaflet and its chordal attachments to the infundibulum.

Carpentier has classified Ebstein's anomaly in the following manner [11].

Type A: The anterior leaflet has normal morphology and the RV is adequate.

Type B: The anterior leaflet has abnormal chordae but normal mobility. Adequate but reduced RV volume.

Type C: The anterior leaflet has restricted motion. Small functional RV with a large atrialized component.

Type D: Also called 'tricuspid sac' as the leaflets form a complete sac of fibrous tissue adherent to the RV. The infundibulum is the only functional portion of the RV.

Pathophysiology

Neonates are symptomatic as a result of ineffective RV cardiac output. This results from a combination of factors including: poor myocardial contractility, severe TV regurgitation, impedance of antegrade pulmonary blood flow across the pulmonary valve, or pulmonary insufficiency. Cardiomegaly is present and can be quite severe, leading to compression of the lungs (Fig. 107.1). In the symptomatic neonate cyanosis is present. RV dysfunction and tricuspid regurgitation causes right to left shunting across the ASD leading to cyanosis. In addition, cyanosis may result from either anatomical or "functional" pulmonary atresia. PVR in the neonatal period is elevated. The diminutive and myopathic RV may not be able to generate enough contractile force to overcome the PVR, as a result, antegrade flow into the pulmonary arteries is impeded, despite the existence of a pulmonary valve with luminal continuity between RV and pulmonary artery. This is referred to as "functional" pulmonary atresia. As such, ductal dependent pulmonary blood flow results. The patient is managed similarly to a single ventricle patient and prostaglandin infusion is utilized for ductal patency. As the PVR drops over the first week of life the RV may then be able to overcome the afterload to establish antegrade flow. True anatomical pulmonary atresia where there is luminal discontinuity between RV and pulmonary artery is seen in 50% symptomatic neonates with EA [5].

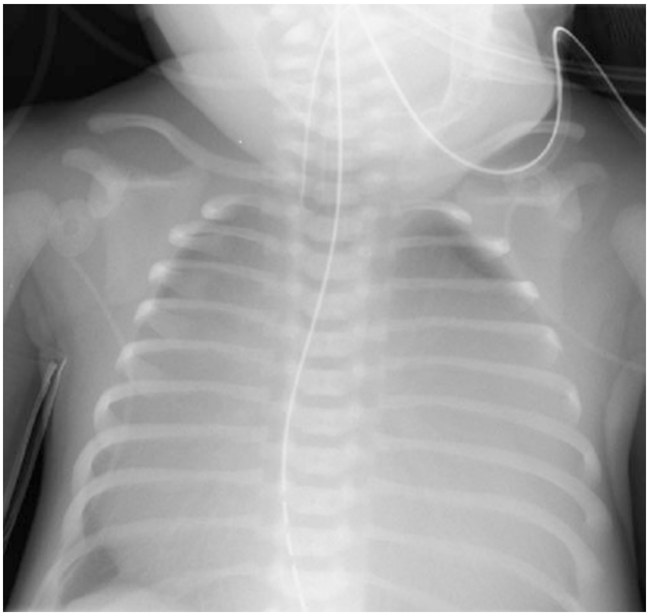


Fig. 107.1 Chest X-ray demonstrating severe cardiomegaly in a newborn with Ebstein's anomaly

Pulmonary regurgitation represents the end-stage of RV failure. A circular shunt is created with left-to-right flow from aorta to pulmonary artery across the PDA to the pulmonary artery. Flow reversal across the pulmonary valve into the RV then occurs. This blood is then ejected into the right atrium due to tricuspid insufficiency and across the ASD to the left side of the heart and the aorta, to complete the circular shunt. Furthermore, this volume overload impedes left ventricular function. This is related to left ventricular displacement of the interventricular septum as a result of the severely dilated dysfunctional RV. "Pancaking" of the LV cavity impedes filling and diminishes systemic cardiac output. Cardiogenic shock then results.

In less severe forms of EA the RV can generate effective antegrade flow especially when the PVR decreases. Antegrade flow across the RV outflow tract is accompanied by clinical improvement in symptoms. Neonates with severe tricuspid regurgitation or gross cardiomegaly who are otherwise asymptomatic have an associated mortality of 45% within the first year of life without intervention [12, 13]. The natural history of being diagnosed with EA during the perinatal period is associated with a high mortality during infancy [4, 14]. Those who survive early childhood can expect reasonable longevity. When the disease is mild, symptoms are not noticed until later in adult life.

Diagnostic Evaluation

Chest X-Ray

Depending on the severity of disease, the chest roentgenograms usually demonstrates massive cardiomegaly with decreased pulmonary vascular markings (Fig. 107.1). Cardiomegaly is a risk factor for need for surgical intervention or mortality.

Electrocardiography

The abnormal development of the TV in EA results in several activation abnormalities including delayed intra-atrial conduction, right bundle branch block (RBBB) in 75–95% and ventricular pre-excitation in 5–25%. As such, the electrocardiogram (ECG) for patients with EA is abnormal. The most common findings are tall P waves and RBBB. EA is the most common congenital heart defect associated with WPW syndrome. When present a characteristic delta wave can be seen on ECG [15].

Echocardiography

EA is diagnosed with echocardiography. Two dimensional (2D) echocardiography can evaluate the TV leaflets and their excursion. From a surgical perspective there are two views that are critical for assessing the valve particularly when considering a two ventricular repair; the apical four chamber and the parasternal short axis (Figs. 107.2 and 107.3). The apical four chamber view allows assessment of leaflet displacement. The distance from the true septal annulus to the level of the apically displaced septal leaflet hinge point defines EA. A distance of ≥8 mm/m^2 is consistent with EA [16]. In addition, leaflet mobility and degree of tethering can be evaluated from this view. Color Doppler is used to evaluate the degree of TV regurgitation. Note the severity of regurgitation can be difficult to quantify due to apical displacement. RV function is also evaluated from this view. The parasternal short axis view assesses for functional or anatomic pulmonary atresia utilizing 2D and color echocardiography. In addition, this view is used to evaluate the size of the functional RV. If the anterior leaflet is engaged into the outflow tract and it is in close proximity to the pulmonary valve then the RV is deemed diminutive. It is unlikely that a two ventricular repair can be achieved when this exists.

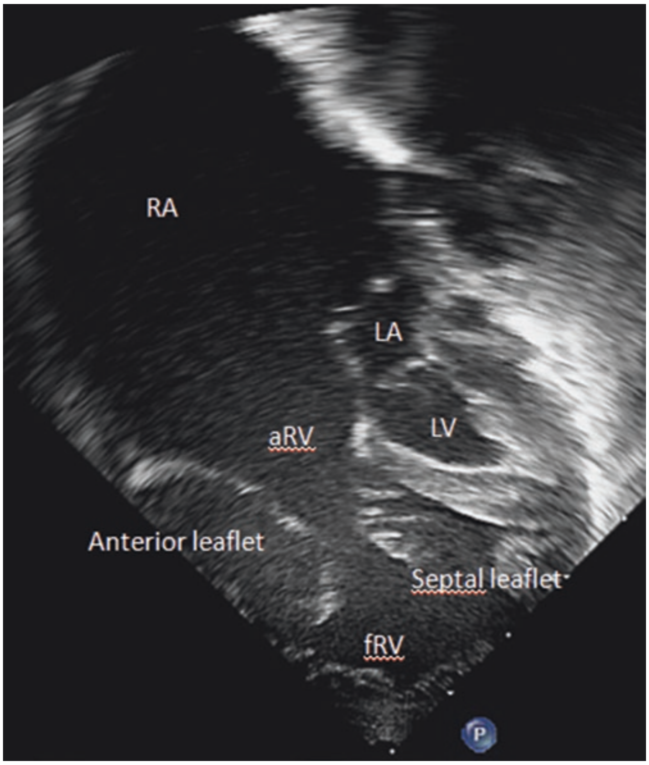


Fig. 107.2 Echocardiogram illustrating the apical four chamber view in Ebstein anomaly. *RA* right atrium, *aRV* atrialized right ventricle, *fRV* functional right ventricle, *LA* left atrium, *LV* left ventricle

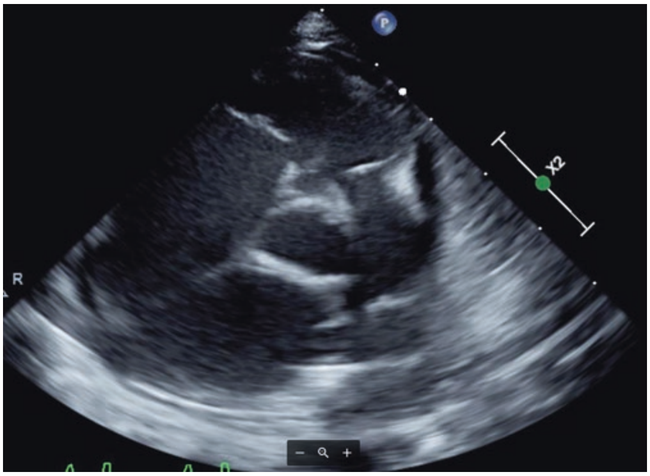


Fig. 107.3 Echocardiogram illustrating parasternal short axis view in Ebstein anomaly. The anterior and septal leaflets are displaced into the right ventricular outflow tact. *AL* anterior leaflet tricuspid valve, *SL* septal leaflet tricuspid valve, *PV* pulmonary valve

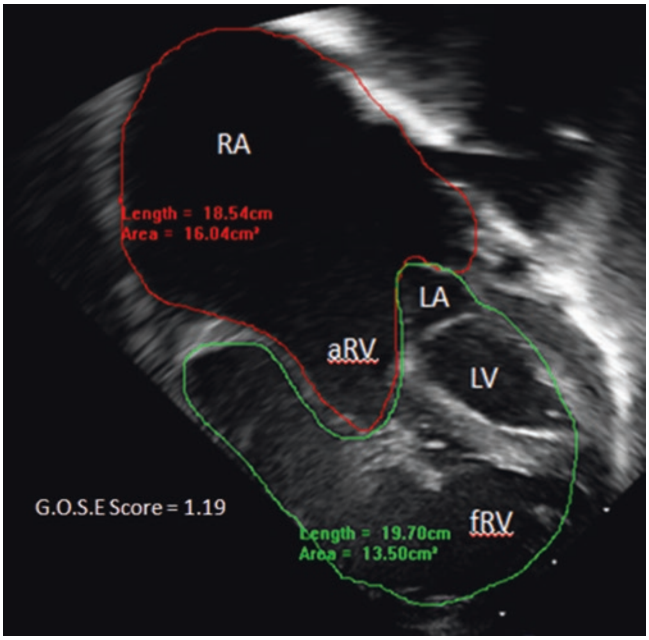


Fig. 107.4 Calculation of the Great Ormond Street Echocardiogram (GOSE) Score: Right atrium (RA) + atrialized Right ventricle (aRV)/Left atrium (LA) + left ventricle (LV) + functional Right ventricle (fRV)

Table 107.1 Mortality prediction based on Great Ormond Street Echocardiography Score

Great Ormond Street Echo (GOSE) score		
GOSE score	Ratio	Mortality
I	<0.5	8%
II	0.5–1.0	8%
III (acyanotic)	1.1–1.4	10% early, 45% late
III (cyanotic)	1.1–1.4	100%
IV	>1.5	100%

Celermajer DS, Bull C, Till JA, et al. J Am Coll Cardiol 1994:22:170–176

The Great Ormond Street Echocardiogram (G.O.S.E.) score is a mortality risk stratification score for neonates with EA. It is calculated from the apical four chamber view by adding the right atrium and atrialized RV volume and dividing by the sum of the functional RV volume, left atrial and ventricular volumes (Fig. 107.4). A G.O.S.E score of 3 (ratio of 1.1–1.4) with cyanosis or 4 (ratio >1.5) has a mortality of nearly 100% [13] (Table 107.1).

Catherization/Computed Tomography/Magnetic Resonance Imaging

There is limited utility for the use of computed tomography, magnetic resonance imaging, or cardiac catheterization in neonatal EA.

Treatment

Medical

The overall hospital mortality for the symptomatic neonate with EA approximates 25% [17]. Furthermore, surgical intervention across the US hospitals is associated with a mortality of 27–36% depending on the procedure performed [17]. There is significant improvement in surgical outcome if the patient can be medically managed out of the neonatal period [18]. As such, in the neonate with EA medical management with supportive care is crucial for improving long term survival. Relatively stable patients can be treated with supplemental oxygen and prostaglandin infusion if functional or anatomical pulmonary atresia is suspected, similar to managing single ventricle physiology. As the PVR decreases, prostaglandin therapy can be discontinued. The adequacy of antegrade flow can be assessed with a diminutive or closed ductus. Once antegrade flow across the pulmonary valve is established, promotion of flow can be facilitated with pulmonary vascular reducing agents and inotropes such as inhaled nitric oxide and milrinone respectively. Management at this stage has now transitioned to a two ventricle physiology. In unstable patients, promoting pulmonary blood flow is important, thus sedation, paralysis, prostaglandin infusion, and inhaled nitric oxide are utilized to decrease PVR. Intubation and mechanical ventilation with large tidal volumes are keys to promoting adequate ventilation in patients with massive cardiomegaly. Inotropic support may be necessary to assist with cardiac output. Figure 107.5 illustrates our algorithm in managing the neonate with EA.

Frequent echocardiograms during the first week are useful to assess antegrade flow across the RV outflow tract, degree of TV regurgitation and RV function. This assessment will help guide weaning prostaglandins, nitric oxide and inotropes. The goal of medical therapy is to be able to discharge the patient and potentially delay the operation outside of the neonatal period where mortality is highest.

Surgical Indications

There are certain neonates and young infants that require surgical repair despite best medical management (Fig. 107.5). These include those patients who are unable to wean from mechanical ventilatory support, failure to wean off prostaglandin or maintain systemic oxygen saturation above 75% while extubated. Other indications include, right heart failure manifested by intolerance to feeds, ascites or pleural effusions and inotropic dependency. Patients with anatomical pulmonary atresia will require as a minimum a reliable source of pulmonary blood flow in the form of a systemic-pulmonary shunt during the neonatal period. In

Fig. 107.5 Algorithm for initial management of Ebstein's anomaly in neonates. *O_2* oxygen, *PVR* pulmonary vascular resistance, *PGE_1* prostaglandin, *iNO* inhaled nitric oxide

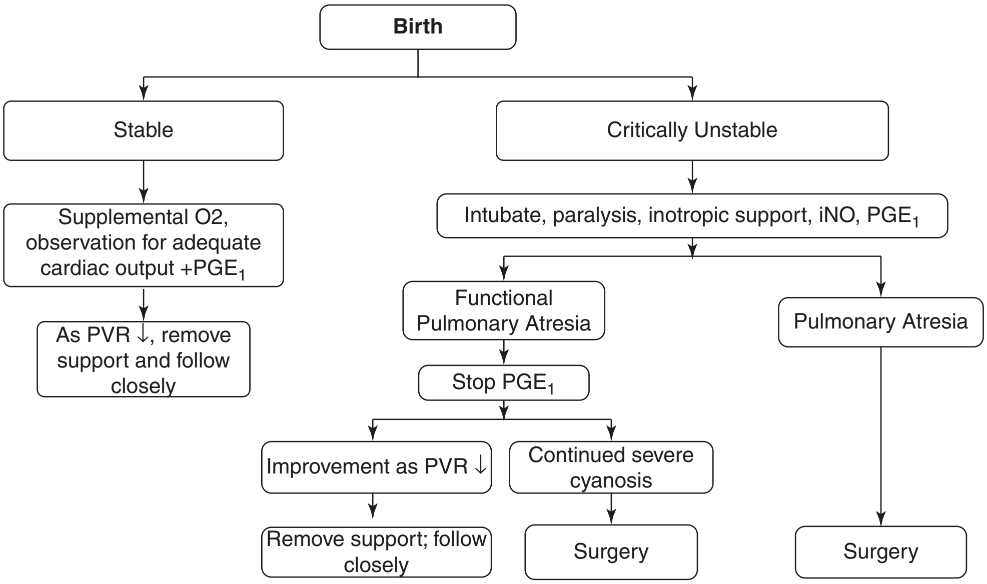
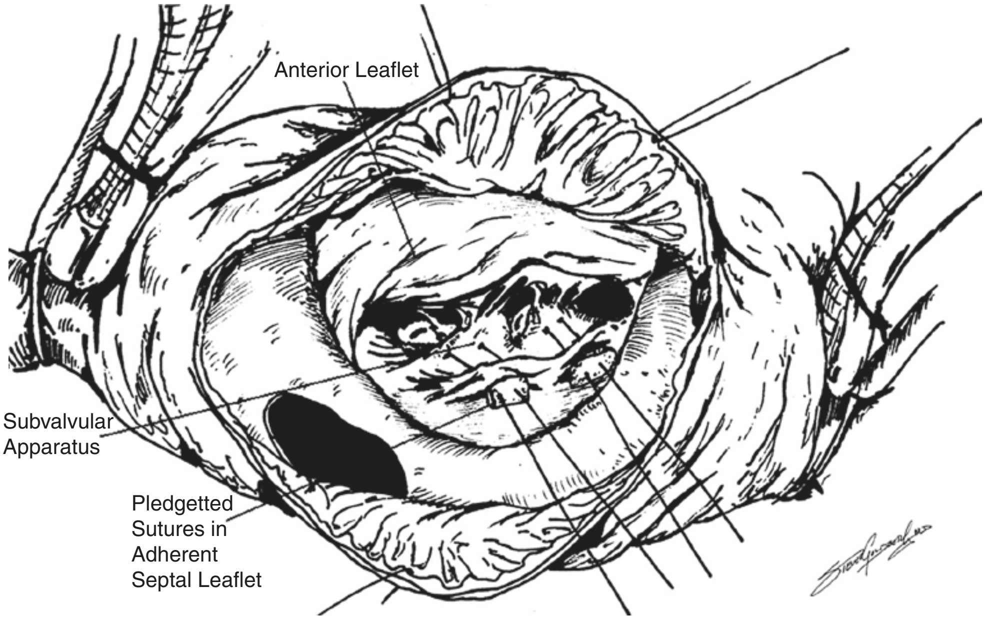

Birth
Stable
Critically Unstable
Supplemental O2, observation for adequate cardiac output +PGE_1
Intubate, paralysis, inotropic support, iNO, PGE_1
As PVR ↓, remove support and follow closely
Functional Pulmonary Atresia
Pulmonary Atresia
Stop PGE_1
Improvement as PVR ↓
Continued severe cyanosis
Remove support; follow closely
Surgery
Surgery

Fig. 107.6 Sebening suture is demonstrated. A suture is passed from the dominant papillary muscle attached to the anterior leaflet and fixed to a point on the ventricular septum directly opposite to move the anterior leaflet to the septum, allowing for coaptation with the septum and/or posterior leaflet


Anterior Leaflet
Subvalvular Apparatus
Pledgetted Sutures in Adherent Septal Leaflet

general, a neonate with a Great Ormond Street Echocardiography (G.O.S.E.) score of 4 or cyanotic and a GOSE score of 3 is highly predictive of early surgical intervention [13].

Surgical Procedures

There have been numerous procedures described for the surgical treatment of neonatal EA [11, 19–29]. Danielson, in 1979, first described some of the essential principles for EA repair in any age group [18]. This includes plication of the atrialized RV, posterior tricuspid annuloplasty, closure of ASD and right atrial reduction atrioplasty. These principles are still utilized. Carpentier's repair advocated RV plication in a longitudinal direction in an attempt to improve RV functional volume by preserving the base to apex dimension. Furthermore, the anterior leaflet is detached, rotated clockwise and reattached to the annulus followed by an annuloplasty ring for durability of repair [11].

The Sebening stitch was introduced in 1997 and remains a very useful technique for establishing TV competency (Fig. 107.6). The dominant anterior papillary muscle is mobilized and transferred towards the interventricular septum. This allows the anterior leaflet to coapt with the ventricular septum or remnant septal or posterior leaflets [22]. We utilize this stitch not infrequently to provide stability and durability of the repair.

The most recent surgical repair is the cone reconstruction, first described by da Silva and colleagues [20]. In this procedure, surgical delamination of the anterior and posterior leaflets of the TV is performed, mobilizing the leaflets from their attachments to the RV leaving only attachments to the leaflet free edge. Leaflets are then rotated clockwise and then reattached to the true annulus. This technique is reproducible and durable in older children and adults [20]. Application of the cone procedure as a biventricular repair for neonatal EA continues to evolve. There are a few reports of the procedure being successfully performed in neonates [24, 25, 28].

Single ventricle palliation in the form of a right ventricular exclusion procedure is performed in neonates in whom a TV repair cannot be achieved or there is inadequacy of the RV. Anatomical pulmonary atresia when present is also a consideration by some for single ventricle palliation. RV exclusion also referred to as a Starne's procedure consists of a fenestrated patch closure of the tricuspid valve, an atrial septectomy allowing for adequate mixing, and a modified Blalock-Taussig-Thomas shunt as a source of regulated pulmonary blood flow [21]. These patients subsequently will require further single ventricle palliation with a bidirectional Glenn and Fontan procedures at around 6 months and 3 years of age respectively.

Knott-Craig has pioneered an innovative approach for biventricular repair for neonates with EA [19, 29]. The guiding principles of this approach include:

1. Monocusp repair based on a mobile anterior leaflet to establish a competent TV.
2. Reduction annuloplasty of the dilated TV annulus.
3. Fenestrated closure of ASD—allows for right to left shunting in the presence of RV dysfunction following repair.
4. Right atrial reduction atrioplasty to improve atrial transport and to reduce extrinsic compression of the lungs.
5. Repair of all associated cardiac defects.

Biventricular repair of neonatal EA utilizes a variety of previously described approaches to create a competent TV from the anterior leaflet, reduce the right atrial volume to remove the compression off the lungs and to facilitate atrial transport, fenestrated closure of the ASD, and repair of other congenital heart defects.

The operation is performed utilizing cardiopulmonary bypass with bicaval cannulation, at moderate hypothermia (28 °C). Cardiac arrest is induced to create a motionless and bloodless field to facilitate exposure and technical efficiency. The TV is exposed via a right atriotomy. The TV and subvalvular apparatus is evaluated. The anterior leaflet is evaluated for size, mobility and fenestrations. The monocusp repair requires a broad anterior leaflet that is mobile with a leading edge that is not tethered.

Once an adequate mobile anterior leaflet is assessed or surgically developed then competency is established by reducing the annulus. Most often this can be accomplished by initially creating a double orifice valve by passing a horizontal mattress suture between the antero-posterior commissure and the coronary sinus. This suture is passed through the anterior wall of the coronary sinus to avoid injuring the conduction tissue. The posterior orifice is then plicated from anterior to posterior annulus (Fig. 107.7). During this maneuver care must be taken to avoid injury to the right coronary

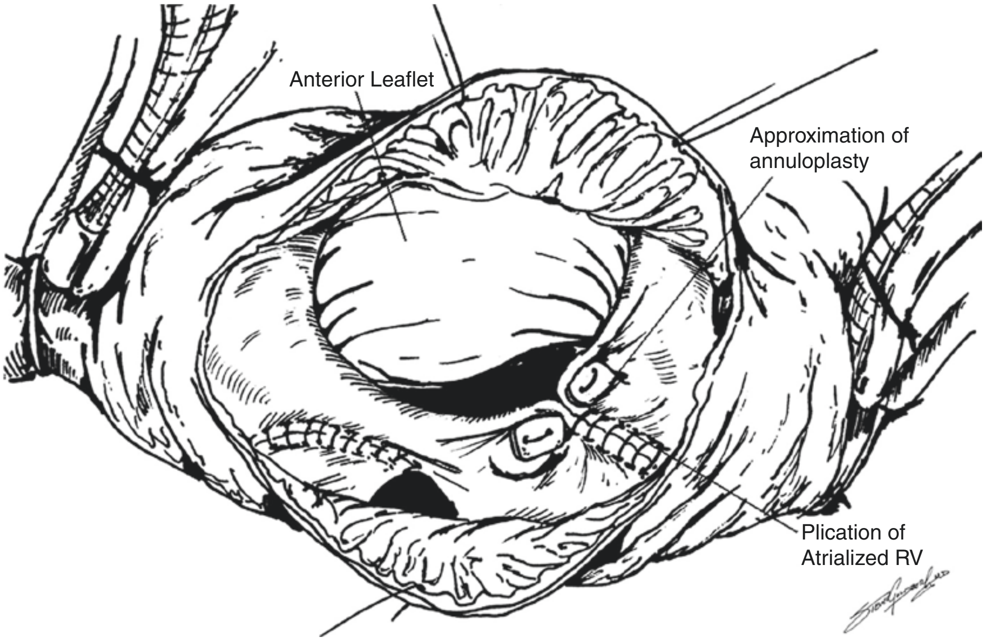


Fig. 107.7 Monocusp repair in the presence of a large mobile anterior leaflet. A double orifice is created by passing a suture through the annulus at the anteroposterior commissure and then through the septal annulus adjacent to the coronary sinus. The posterior annulus and right ventricle is then plicated. *ASD* atrial septal defect, *RV* right ventricle

artery. The annulus can also be reduced utilizing a De Vega annuloplasty from the antero-septal to postero-septal commissure.

If there is tethering of the anterior leaflet then it is detached from its annulus and the attachments surgically delaminated to mobilize the leaflet. The posterior annulus is reduced as previously described and the anterior leaflet is then reattached to the annulus (Fig. 107.8).

In rare circumstances, there is a deficiency of anterior leaflet tissue to establish a competent monocusp. In such cases the anterior leaflet is augmented by detaching it from the annulus and interposing an autologous pericardial patch between annulus and leaflet tissue (Fig. 107.9). The ASD is closed with a patch of autologous pericardium. A 3–4 mm fenestration is essential to act as a right to left shunt. This is useful postoperatively since RV dysfunction is not infrequently present and this shunt maintains cardiac output at the expense of a more cyanotic patient. The free wall of the right atrium is widely excised for the reduction atrioplasty.

All associated cardiac defects are addressed. Most commonly anatomic pulmonary atresia is seen in approximately 60% of neonates with EA that we have treated. Based on our experience we now choose to place a RV-pulmonary artery valved conduit [17] (Fig. 107.10). Pulmonary valve competency is important to the myopathic RV. In addition, it alleviates the volume load on the TV repair.

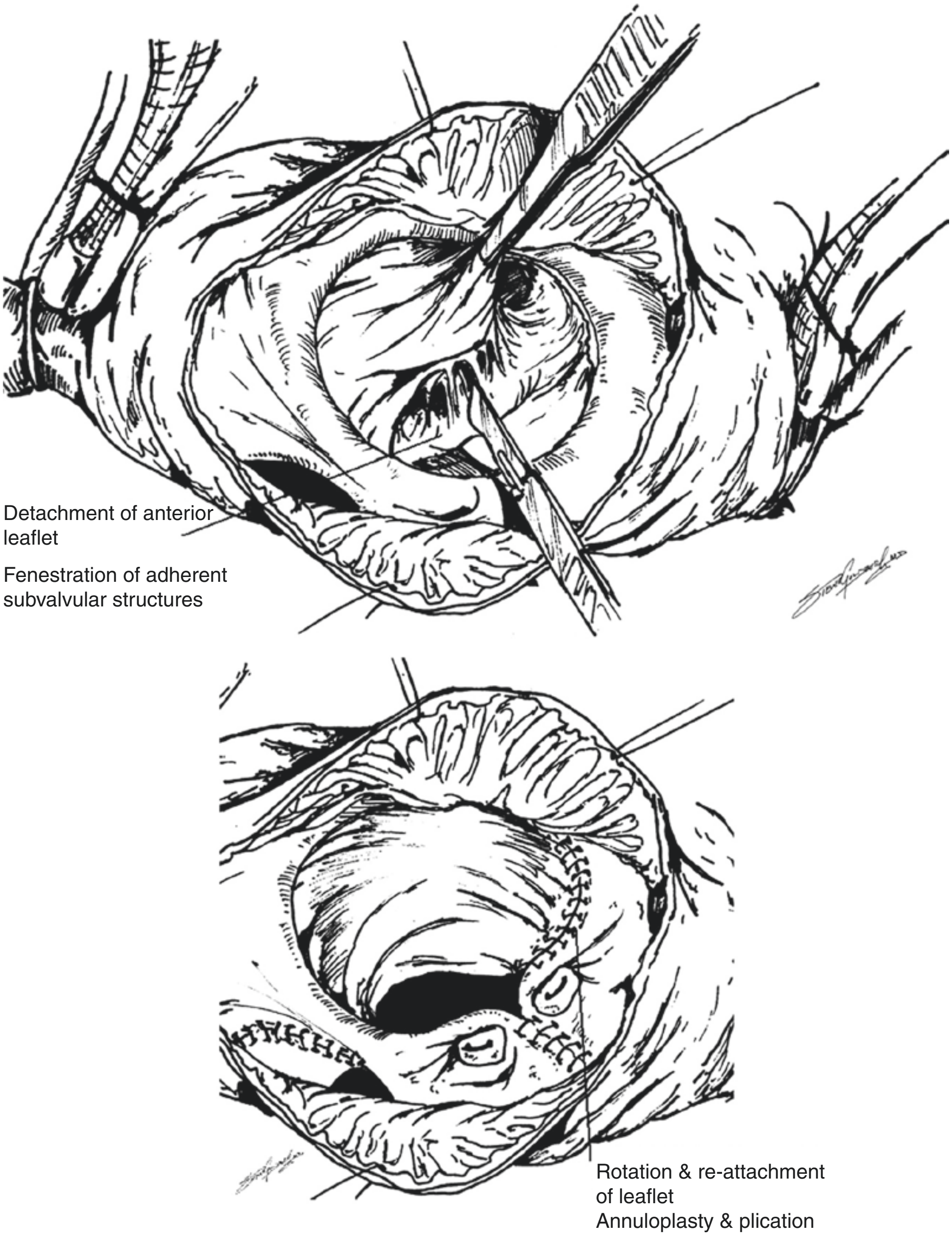

Detachment of anterior leaflet
Fenestration of adherent subvalvular structures
Rotation & re-attachment of leaflet
Annuloplasty & plication

Fig. 107.8 Monocusp repair in the presence of a tethered anterior leaflet. The anterior leaflet is detached from its annulus and surgically delaminated. The posterior annulus is reduced. The anterior leaflet is then rotated and reattached to the annulus

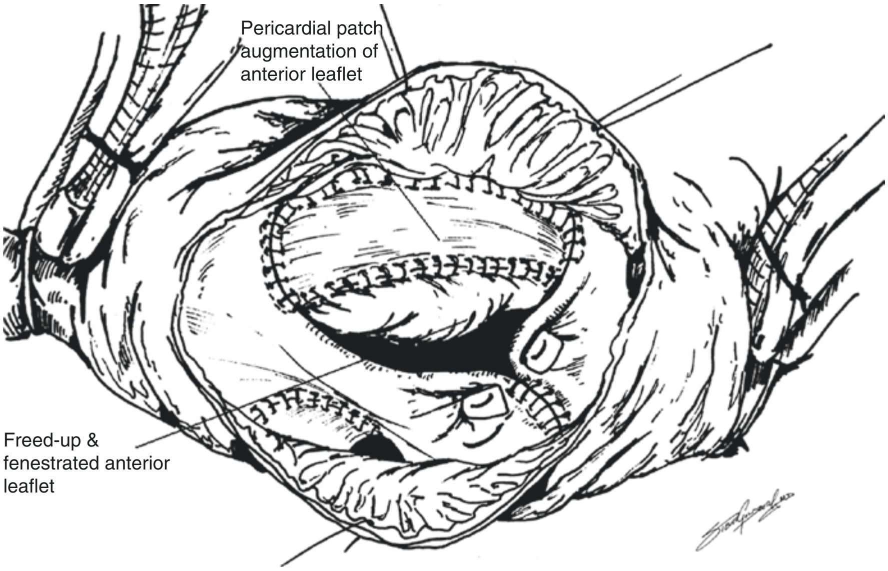

Pericardial patch augmentation of anterior leaflet
Freed-up & fenestrated anterior leaflet

Fig. 107.9 Monocusp repair in the presence of a tethered and small anterior leaflet. The anterior leaflet is detached from its annulus and surgically delaminated. The posterior annulus is reduced. The anterior leaflet is augmented by interposing autologous pericardium between the annulus and the detached leaflet

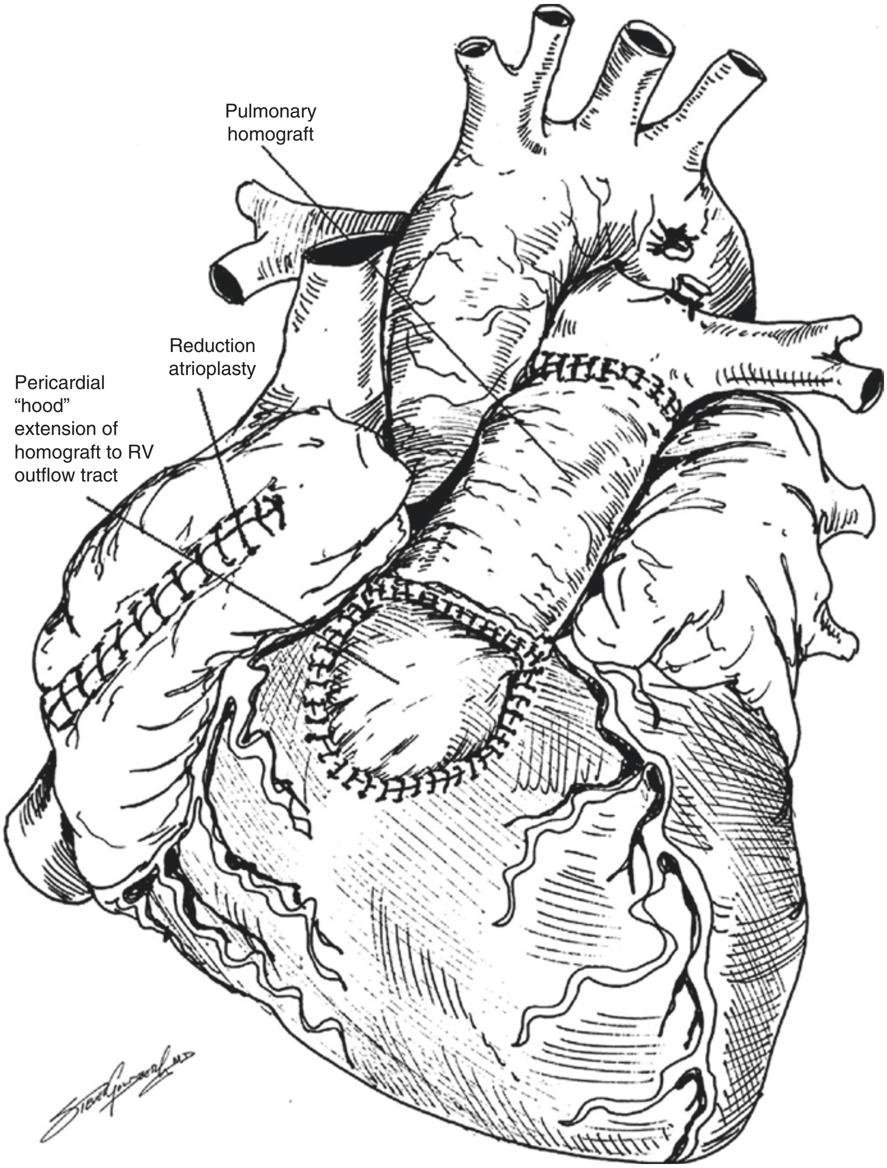

Pulmonary homograft
Reduction atrioplasty
Pericardial "hood" extension of homograft to RV outflow tract

Fig. 107.10 Biventricular repair for neonates with pulmonary atresia. Right ventricle-pulmonary artery conduit is utilized

Furthermore, although a biventricular repair can be achieved most of the time with EA, we do however recognize the learning curve associated with this operation and that a Starnes stage I palliation should be considered in the presence of anatomical pulmonary atresia or severely hypoplastic functional RV.

Outcomes

Controversy exists as to the surgical strategy for the symptomatic neonate. Mizuno et al. described their center's experience with neonatal EA repair. Their results demonstrated greater survival in biventricular repair versus single ventricle palliation, 60% versus 25% [24]. A recent follow up study by Kumar et al. evaluated the median 7 year follow up for the Starnes procedure in 27 neonates [23]. Their overall survival was 81% ± 5%. Boston et al. described neonatal biventricular repair outcomes for EA [18]. In this series biventricular repair was achieved in 90% of the cohort. Overall, early survival was 78.1% while the 15 year survival estimate was 40% ± 15% versus 79% ± 13% in neonatal repairs with or without anatomical pulmonary atresia [18]. Furthermore, the monocusp repair is durable with most patients remaining with mild tricuspid regurgitation. To date only two of the patients who underwent TV repair have undergone TV replacement. Furthermore, Huang et al. utilized a staged approach to accomplish biventricular repair in neonates with EA. In this approach an initial TV repair utilizing the cone procedure along with a small BT shunt for pulmonary stenosis or large ASD for inadequate RV achieved an 86% survival over a median follow-up of 4.5 years [25]. As such biventricular repair can now be accomplished with good survival allowing for the benefits of two-ventricle physiology.

Conclusion

Neonatal EA continues to be a challenging surgical problem. Surgical approaches for the management of these critically ill neonates have varied across institutions. Biventricular repair for neonatal EA provides good long-term survival and freedom from reoperation, particularly in those patients in whom a competent TV repair is achieved.

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108

Vascular Rings and Pulmonary Artery Sling

Carl L. Backer

High Yield Facts

- Vascular rings are congenital vascular anomalies of the aortic arch system which compress the esophagus and trachea.
- The two major categories of vascular rings are double aortic arch and right aortic arch with left ligamentum.
- Pulmonary artery (PA) sling occurs when the left pulmonary artery originates from the right pulmonary artery and then courses between the esophagus and trachea en route to the left lung.
- PA sling patients frequently have associated tracheal stenosis secondary to complete cartilaginous tracheal rings.
- The presentation of a child with a vascular ring relates directly to the degree of compression of the trachea and/or esophagus.
- For patients with a PA sling the majority of symptoms are often related to the associated tracheal stenosis.
- Computed tomography is the diagnostic investigation of choice.
- Presence of symptoms is an indication for intervention.
- Vascular rings are repaired through a thoracotomy with division of the ligamentum, division of the smaller of the two aortic arches for double aortic arch, and resection of a Kommerell diverticulum if present.
- PA slings are repaired through median sternotomy with cardiopulmonary bypass. Simultaneous repair of associated intracardiac lesions and slide tracheoplasty for congenital tracheal stenosis are performed.

Introduction

Vascular rings are congenital vascular anomalies of the aortic arch system which compress the esophagus and trachea. The two major categories of vascular rings are double aortic arch and right aortic arch with left ligamentum. In both cases the trachea and esophagus are encircled by either vascular or ligamentous structures which cause symptoms related to those two structures. Pulmonary artery (PA) sling occurs when the left pulmonary artery originates from the right pulmonary artery and then courses between the esophagus and trachea en route to the left lung. PA sling patients frequently have associated tracheal stenosis secondary to complete cartilaginous tracheal rings.

The first surgical repair of a vascular ring was by Dr. Robert Gross at Boston Children's Hospital [1]. He successfully divided a double aortic arch in a 1-year-old child with persistent wheezing and recurring hospital admissions for upper respiratory tract infections. Gross was also the first to describe division of the left ligamentum for patients with a right aortic arch and left ligamentum. A recent contribution of our group has been to emphasize the importance of an associated Kommerell diverticulum, which can independently compress the trachea and esophagus [2]. Removal of this diverticulum is now seen as an important part of the operation for many of these patients.

Dr. Willis J. Potts (from our institution) was the first surgeon to correctly diagnose and successfully repair a patient with a pulmonary artery sling [3]. The classification scheme for vascular rings that we have used is the one endorsed by the Society of Thoracic Surgeons Congenital Nomenclature and Database Committee [4]. Our experience with vascular rings at Ann & Robert H. Lurie Children's Hospital of Chicago is illustrated in Table 108.1.

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Vascular Rings

Natural History and Clinical Presentation

The presentation of a child with a vascular ring relates directly to the degree of compression of the trachea and/or esophagus. For neonates and infants noisy breathing and a "barky" cough are the most common initial symptoms. Dysphagia related to esophageal compression typically does not occur until after the child attempts to eat solid foods. Other symptoms include recurrent upper respiratory tract infections, wheezing, croup, dyspnea on exertion, apnea, and even apparent life-threatening events.

For patients with a pulmonary artery sling the majority of symptoms are often related to the associated tracheal stenosis. These patients may develop respiratory distress and even require intubation. Attempts at intubation may be marked by difficulty passing a normal sized endotracheal tube due to the tracheal stenosis. These patients also have bronchomalacia where the left pulmonary artery encircles the right bronchus.

Older patients with vascular rings have often learned to live with the chronic respiratory issue. However, the dysphagia can become severe over time. Older children have often learned to chew their food quite carefully and drink an excessive amount of water to help wash the food down.

It is important to have a high index of suspicion for this diagnosis. We have cared for occasional patients, who despite having many of the above symptoms, have spent weeks if not months being hospitalized for recurrent pneumonia and upper respiratory tract infections.

Table 108.1 Lurie Children's Experience 1947–2018

Pathology	# of Patients
Vascular ring	
Double aortic arch	187
Right aortic arch/left ligamentum	217
Pulmonary artery sling	47
Total	451

Diagnostic Techniques

Over the past 30 years there has been a dramatic evolution in the diagnostic strategies for patients with vascular rings [5]. If the history is suggestive of a vascular ring the first diagnostic study is the chest radiograph. "Normal" patients have a prominent left aortic arch "knob." Patients with a right aortic arch will have the same knob on the *right* side and often careful visualization of the trachea will demonstrate compression on the right side of the trachea. For patients with a double aortic arch it is often difficult to determine whether the arch is right or left-sided. This is a clue to the fact that the patient might have a double aortic arch. Thirty years ago a barium esophagram was the diagnostic procedure of choice. This has been completely supplanted by the use of computed tomographic (CT) imaging. The actual evaluation is completed in less than 1 s without the need for intubation and now with a considerable reduction in the radiation dose. Some centers prefer magnetic resonance imaging (MRI) because it does not involve the use of radiation. However, the MRI requires a longer period of time to obtain and often requires that the patient be intubated for the procedure. In addition, the MRI currently does not offer as accurate an image of the tracheal anatomy. Figure 108.1a, b is a computed tomogram of a child with a double aortic arch. Figure 108.2a, b is a computed tomogram of a child with a right aortic arch, retroesophageal left subclavian artery, left ligamentum, and large Kommerell diverticulum.

The preoperative imaging is extraordinarily helpful in devising a plan prior to beginning the operation. No longer does the surgeon have to carefully investigate the intraoperative anatomy to make a decision of where to divide the vascular ring.

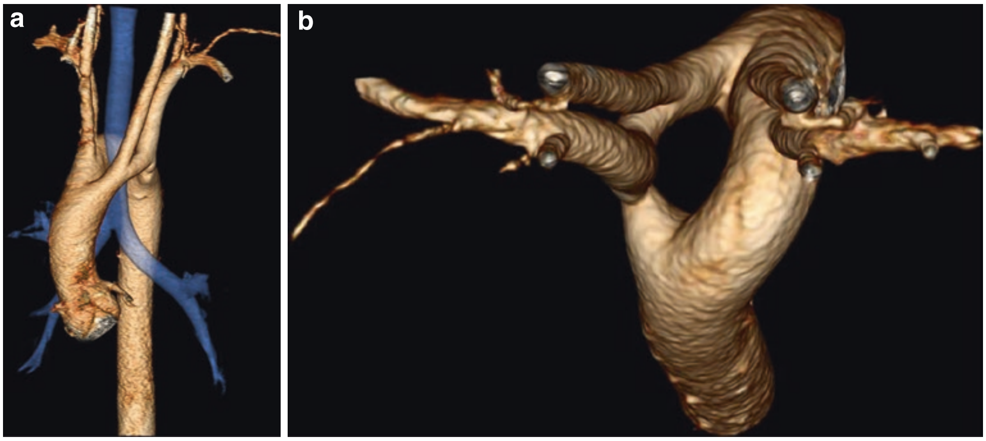

Fig. 108.1 Computed tomogram of child with a double aortic arch. (**a**) Frontal view of 3D reconstruction. Airway is ghosted in blue. The right arch is dominant. The left arch is smaller but patent. There is also a left ligamentum that is not seen. (**b**) Superior view illustrates the complete vascular ring formed by all patent vascular structures

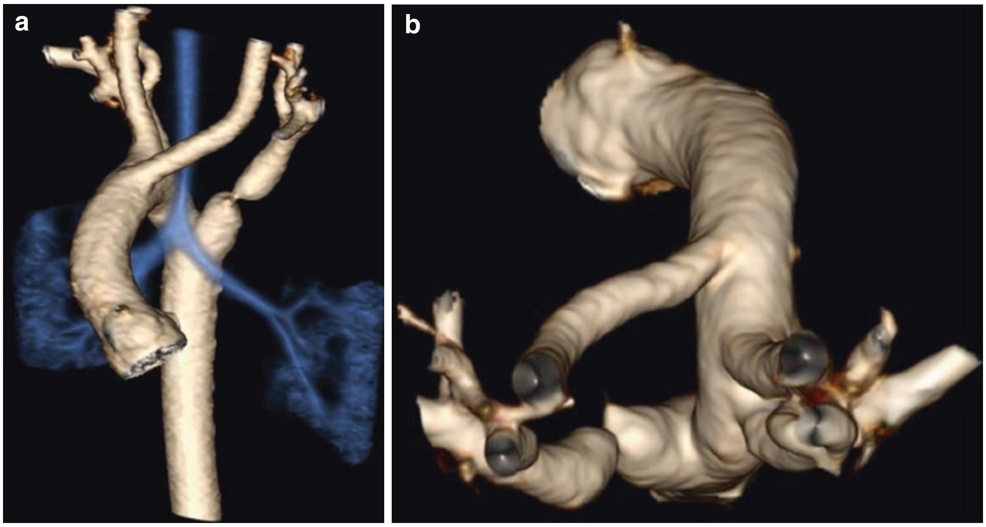

Fig. 108.2 Computed tomogram of child with a right aortic arch, retroesophageal left subclavian artery, left ligamentum, and Kommerell diverticulum. There is a stenosis of the origin of the left subclavian artery. (**a**) Frontal view of 3D reconstruction. Airway is ghosted in blue. (**b**) Superior view illustrates the complete vascular ring completed by the ligamentum (not visible). Note that the area within the "ring" is larger than the patient with a double aortic arch (Fig. 108.1b)

Another avenue of potential diagnosis is the child who presents to the otolaryngology service with noisy breathing or a chronic cough. These patients often undergo a bronchoscopy as their first examination. This exam in a patient with a vascular ring typically shows extrinsic pulsatile compression of the trachea. This should alert the ENT physician to the potential diagnosis of a vascular ring which would be then confirmed by CT imaging. We also recommend an echocardiogram in these patients. Approximately 12% of patients with a vascular ring will have associated cardiac pathology [5]. In addition, we obtain a bronchoscopic evaluation at the time of operative intervention for all patients with a vascular ring, particularly in patients with a pulmonary artery sling.

Indications for Operation

Any child who is symptomatic and has a vascular ring meets indications for operative intervention. In particular, patients with a double aortic arch and pulmonary artery sling nearly always have symptoms. There are a small number of patients with a right aortic arch and left ligamentum who do not have significant tracheal or esophageal compression. In our service we are simply observing a small number of these asymptomatic patients.

Once the diagnosis of vascular ring is made in a patient who is symptomatic we recommend operative repair soon after the diagnosis. This helps avoid serious complications such as apnea, hypoxic episodes, or a severe upper respiratory tract infection requiring intubation. Other rare complications from unrepaired vascular rings include aortic dissection associated with Kommerell diverticulum, bleeding from an indwelling nasogastric tube eroding into the vascular ring, and slow resolution of tracheomalacia following repair if the diagnosis and operation are delayed substantially. Patients with esophageal compression that is not repaired may not have resolution of their dysphagia after release of the vascular ring due to loss of motility of the esophageal muscular wall.

Operative Techniques

Double Aortic Arch

These patients typically develop symptoms in the first few months of life. There are three main types of double aortic arch: dominant right arch, dominant left arch, and balanced arches. In addition, a small number of patients with a double aortic arch will have a significant associated Kommerell diverticulum. The most common double aortic arch is the right arch dominant. These patients are best approached through a left thoracotomy. Patients with a dominant left arch are best approached through a right thoracotomy. In patients with balanced aortic arches the decision on which arch to divide is greatly facilitated by the preoperative CT imaging. If there is a significant associated Kommerell diverticulum we recommend excision of the diverticulum at the time of intervention [6].

For a patient with a double aortic arch that is right dominant the approach would be through a left muscle sparing fourth intercostal space thoracotomy. The lung is retracted and the pleura overlying the subclavian artery is opened. This incision in the pleura is then carried proximally and distally to expose the mediastinal structures. I prefer to keep the incision somewhat anterior to avoid injuring the thoracic duct which is generally more posterior in the left chest. The vagus nerve, recurrent laryngeal nerve, and the phrenic nerve are all identified and carefully avoided. In sequential order I encircle the left subclavian artery, the ligamentum arteriosum, and the distal left aortic arch. The preoperative CT imaging will identify the portion of the arch that is the smallest and/or atretic. Commonly this is where the distal left aortic arch inserts into the descending thoracic aorta.

The first part of this procedure is to doubly ligate and divide the ligamentum arteriosum. Following this the left aortic arch can be divided between the vascular clamps. This is illustrated in Fig. 108.3a. Staged division and oversewing techniques are used so that the arch does not slip out of the vascular clamp. Hemostasis here is quite important as when the clamps are released the stumps often retract substantially. Once the clamps are released the esophagus can be clearly visualized (Fig. 108.3b). Any bands of scar tissue that have developed around the esophagus should be carefully divided. The mediastinal pleura is always left open to prevent scarring which could lead to recurrence of symptoms. We use a Blake drain to drain the pleural space. This drain is typically left in place for 1–2 days to ensure that there is no postoperative bleeding and no chylothorax. At the conclusion of the case it is very important to have the child extubated on the operating room table. These patients, because of their previous compression of the esophagus and bronchus often have tracheobronchomalacia and will have some retractions and noisy breathing at the time of extubation. The operating room is the best place to observe them after extubation. This may take patience but these patients typically begin to improve over a period of hours after the operation. The average length of stay for a patient with a double aortic arch is 3 days. The parents should be counseled that it may take up to a year for the child's noisy breathing to resolve as the tracheobronchomalacia slowly improves over time.

Since 1947 we have operated on 187 patients for double aortic arch repair. The median age at repair is 1 year of age. There has been no operative mortality since 1952. Two patients have been reoperated on for recurrent symptoms caused by recurrent scar tissue developing at the site of arch division. The incidence of chylothorax is 2%. Ten patients in this series have been noted to have small associated Kommerell diverticulum which was resected [6]. In two patients, resection of the diverticulum required transfer of the left subclavian artery to the left carotid artery. This is explained more thoroughly in the next section on right aortic arch.

Right Aortic Arch

These patients typically present somewhat later in life than patients with a double aortic arch. They generally begin to have symptoms between 2 and 6 months of age. There are two main types of right aortic arch [5]. Two-thirds of the patients have a retroesophageal subclavian artery with a ligamentum (Fig. 108.4a). One-third of the patients with a right

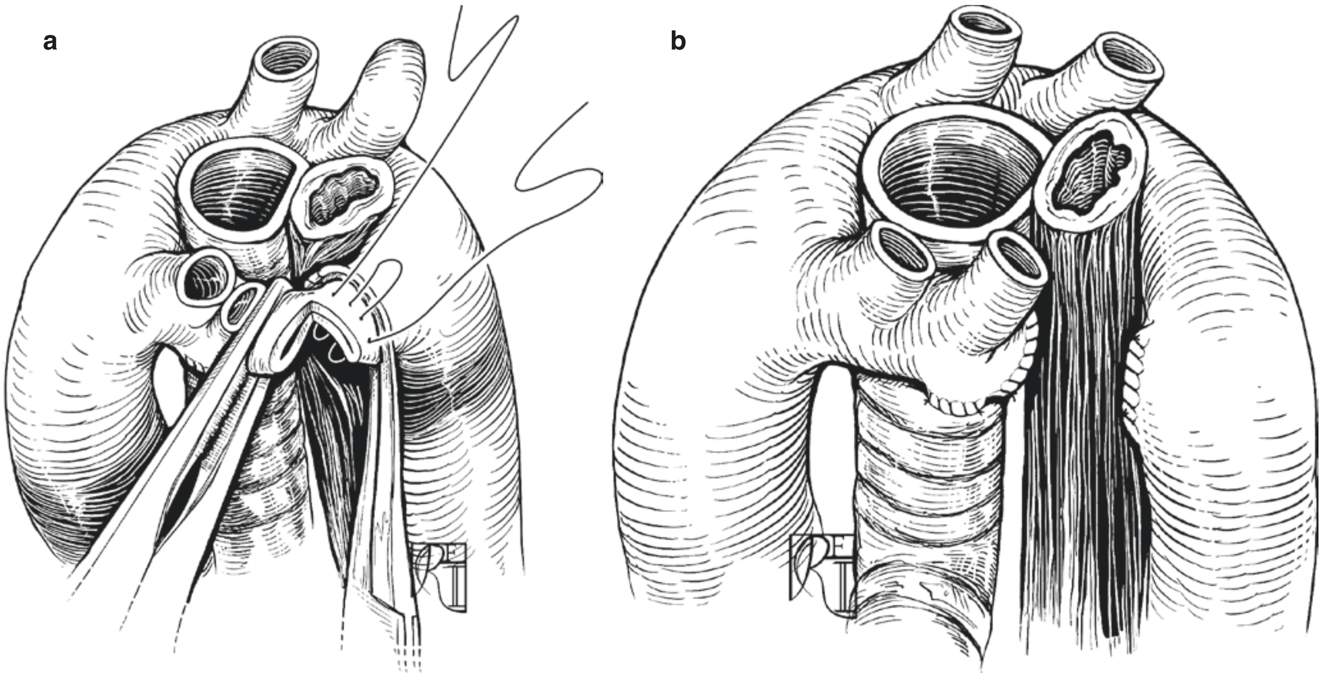

Fig. 108.3 (**a**) Surgical division of a double aortic arch. The distal left aortic arch has been occluded with vascular clamps. The arch has been partially transected and the distal stump is being oversewn with running prolene suture. (**b**) Completed double aortic arch division. The stumps of the divided left arch have been oversewn. The site of ligamentum division was also oversewn. The esophagus is now clearly visible and is no longer compressed. (Reprinted with permission. Backer CL, Mavroudis C. Vascular Rings and Pulmonary Artery Sling. In Mavroudis C, Backer CL [eds]: *Pediatric Cardiac Surgery*, 4th ed., 2013, Oxford, UK, Wiley-Blackwell, pp. 234–255)

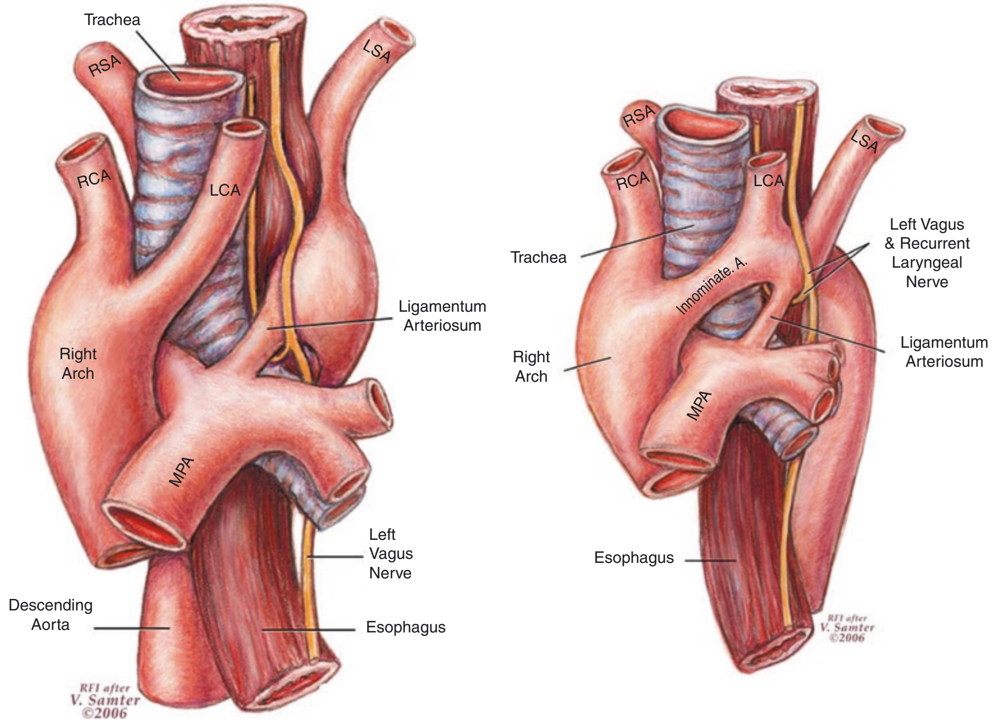

Fig. 108.4 (**a**) Right aortic arch, retroesophageal left subclavian artery, and left ligamentum arteriosum. This forms a complete vascular ring. (**b**) Right aortic arch, mirror-image branching. In this case a vascular ring is not formed because the ligamentum originates from the left innominate artery. *Innominate A* innominate artery, *LCA/RCA* left/right carotid artery, *MPA* main pulmonary artery, *LSA/RSA* left/right subclavian artery. (From: Backer CL, Mavroudis C, Steward RD, Holinger LD. Congenital anomalies: vascular rings. In: Patterson GA, Cooper JD, Deslauriers J, Lerut AE, Luketich JD, Rice TW, [eds]. *Pearson's Thoracic and Esophageal Surgery*, Philadelphia: Church Livingstone Elsevier; 2008, 242–255)

aortic arch have mirror-image branching and the ligamentum arises from the anterior innominate artery (Fig. 108.4b). These patients do not have a vascular ring. A frequent association of patients with right aortic arch is a Kommerell diverticulum. A Kommerell diverticulum is a remnant of the distal fourth aortic arch. This diverticulum can actually enlarge and become an independent cause of external compression of either the trachea, the esophagus, or both. In these patients careful consideration is given to resecting the diverticulum at the time of vascular ring repair [7, 8]. If the left subclavian artery originates from the Kommerell diverticulum the operation is facilitated by transfer of the left subclavian artery to the left carotid artery [9].

These patients are all approached through a muscle-sparing fourth intercostal space left thoracotomy. The lung is retracted, the pleura is opened, and the nerves are identified and preserved. The ligamentum is encircled and then divided between silk ligatures reinforced with prolene sutures. Alternatively the ligamentum can be divided between vascular clamps with oversewing of the stumps. In many cases division of the ligamentum alone is enough to spring the vascular ring apart. The operation is usually successful if the esophagus is then clearly freed and easily visible; no longer compressed by the ligamentum.

However, in a substantial number of patients ligamentum division alone is not sufficient to relieve the tracheal and esophageal compression as they also have a Kommerell diverticulum. We define a substantial diverticulum as one that is more than 1.5 times the size of the subclavian artery distal to the diverticulum. We came to recognize that this diverticulum was a potential significant factor for these patients when we had to reoperate on a number of patients with recurrent symptoms after simple ligamentum division [2]. In these patients their recurrent symptoms regressed when the diverticulum was resected as a second operation.

In these patients the dissection includes encircling the left subclavian artery and the left carotid artery with vessel loops. Figure 108.5a–c shows the operative steps of resection of the Kommerell diverticulum and transfer of the left subclavian artery to the left carotid artery. Prior to applying vascular clamps the patient is given 100 units/kg of heparin intravenously. The base of the Kommerell diverticulum is

lar clamps the patient is given 10

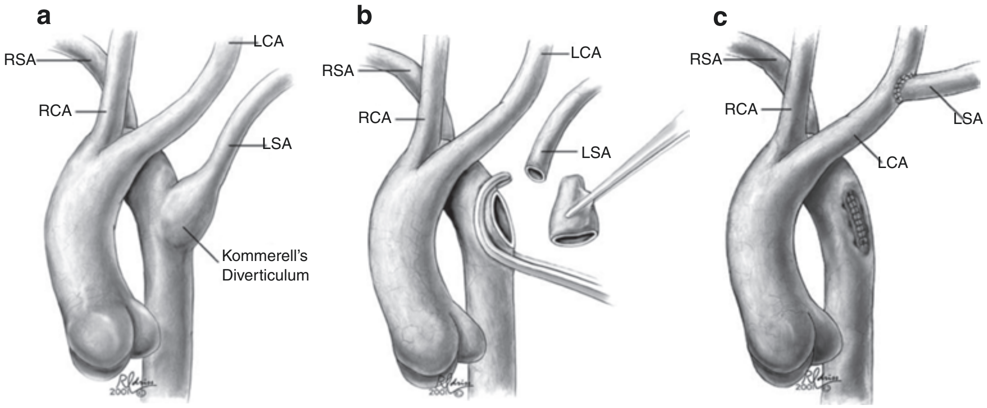

Fig. 108.5 (**a**) Patient with a right aortic arch, retroesophageal left subclavian artery, and large Kommerell diverticulum. (**b**) Resection of a Kommerell diverticulum through a left thoracotomy. There is a vascular clamp partially occluding the descending thoracic aorta at the origin of the Kommerell diverticulum. The Kommerell diverticulum has been completely resected. The clamp on the distal left subclavian artery is not illustrated. (**c**) The completed repair. The orifice where the Kommerell diverticulum was resected is usually closed primarily. The left subclavian artery has been implanted into the side of the left common carotid artery with fine running polypropylene suture. *LCA* left carotid artery, *LSA* left subclavian artery, *RCA* right carotid artery, *RSA* right subclavian artery. (Reprinted with permission: *Eur J Cardiothorac Surg* 2002;22:64–69)

controlled with a Castañeda or Satinsky clamp. The distal subclavian artery is controlled with a small vascular clip or bulldog clamp. The subclavian artery is transected at its origin from the Kommerell diverticulum. The Kommerell diverticulum is then excised, again using staged division and oversewing techniques similar to the techniques used for dividing a left aortic arch. A second clamp is then used to occlude the left carotid artery. During this portion of the procedure it is important to maintain a relatively high arterial perfusion pressure so that the cerebral blood flow is maintained through the Circle of Willis. A linear incision is made in the carotid artery and an end-to-side anastomosis performed with running prolene suture. The anastomosis is sequentially de-aired. The pleura is again left open and the chest is closed with a small Blake drain in position. Just as for patients with a double aortic arch we have emphasized extubation in the operating room for these patients.

Since 1947 we have operated on 217 patients with a right aortic arch and left ligamentum. The median age at the time of operative intervention is 1.5 years. There has been no operative mortality since 1959. Since 2006, 47 patients out of 111 patients with a right aortic arch have undergone resection of a Kommerell diverticulum. This is essentially 40% of the patients we operated on with a right aortic arch. The length of stay for patients with simple ligamentum division has ranged from 2 to 3 days. If the patient requires Kommerell diverticulum excision and left subclavian artery transfer the mean length of stay has been 4.5 days.

Pulmonary Artery Sling

Dr. Willis J. Potts from our institution was the first surgeon to report successful repair of a pulmonary artery sling [3]. The child that Dr. Potts operated on was 5 months old and had multiple intermittent attacks of dyspnea and cyanosis. The only imaging performed prior to the operation was fluoroscopy which demonstrated compression of the right bronchus and distal trachea. Because of this Potts approached the patient through a right thoracotomy! He was able to make the diagnosis intraoperatively and made the decision to divide the left pulmonary artery between Potts ductus clamps and then reimplant the left pulmonary artery to the main pulmonary artery. The child survived the operation and is a long-term survivor. However, on follow-up many years later he was found to have an occluded left pulmonary artery [10]. Following Potts' initial operation in 1954, for many years surgeons attempted to repair left pulmonary artery sling through a left thoracotomy. Unfortunately, many of these patients on late follow-up had either a left pulmonary artery stenosis or occlusion [11]. The solution to this technical issue was to operate on the patient through a median sternotomy with the use of cardiopulmonary bypass, a technique we introduced and have utilized since 1985 [12]. A secondary benefit of this approach is that it facilitates tracheal repair. Two-thirds of the patients with pulmonary artery sling have associated complete tracheal rings causing tracheal stenosis. For these patients tracheal resection or slide tracheoplasty is performed [13]. Associated intracardiac anomalies are also repaired at the time of pulmonary artery sling repair. The pulmonary artery and intracardiac repairs are performed prior to opening the trachea for the tracheal repair.

Clinical Presentation

The presentation of patients with pulmonary artery sling is often more dramatic than patients with other types of vascular rings. The patients with tracheal stenosis often present in severe respiratory distress with the need for emergent resuscitation and intubation. The diagnosis of a patient with pulmonary artery sling is by one of two methods. For the sick patient in the intensive care unit who has been intubated the diagnosis can be made by transthoracic echocardiography at the bedside without moving a critically ill child. For a more stable patient CT imaging is diagnostic and will also reveal the anatomic detail of the trachea and the extent, if present, of tracheal stenosis [5]. For these patients, like the vascular ring patients we recommend a bronchoscopic evaluation just prior to operative intervention.

Operative Techniques

Pulmonary Artery Sling Repair

The pre- and postoperative anatomic findings of pulmonary artery sling repair are shown in Fig. 108.6. After median sternotomy the patient is placed on cardiopulmonary bypass with aortic and uniatrial venous cannulation. The left pulmonary artery is identified originating from the superior aspect of the right pulmonary artery. The left pulmonary artery is mobilized as far as possible underneath the trachea and anterior to the esophagus. The left ligamentum is doubly ligated and divided. The pericardium is opened on the left side of the trachea and the left pulmonary artery identified. This is typically just superior to the left main bronchus and anterior to the aorta. The origin of the left pulmonary artery from the right pulmonary can be controlled with a partial occlusion clamp. The left pulmonary artery is then transected. The stump of the left pulmonary artery is then oversewn with running prolene suture in two layers. Traction on the left pulmonary artery from the left side of the mediastinum and further dissection underneath the trachea causes the left pulmonary artery to come out into the anterior mediastinum. Usually the site for

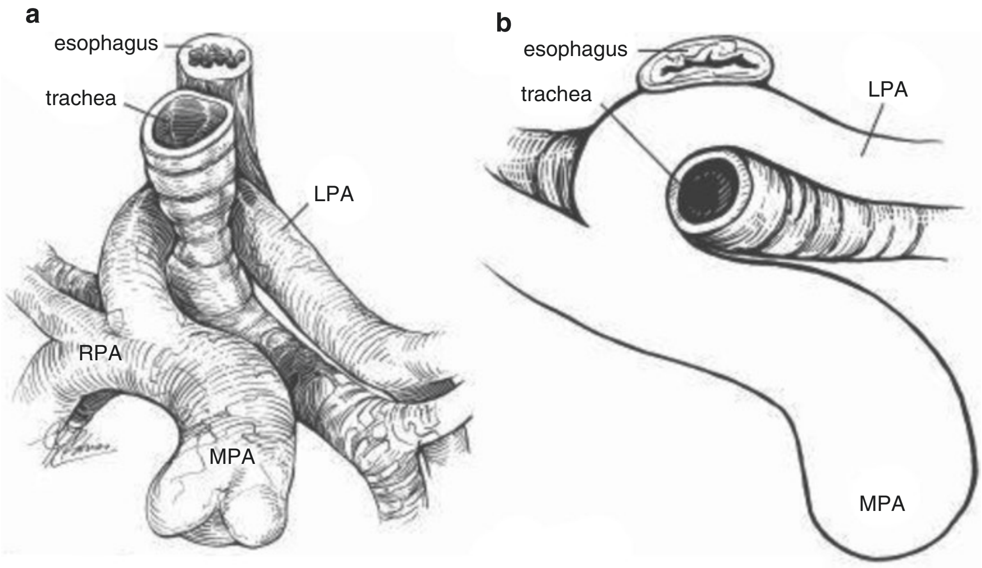

Fig. 108.6 Illustration of operative technique for pulmonary artery sling repair with tracheal resection (performed with cardiopulmonary bypass). (**a**) LPA encircles and compresses distal area of trachea and right main stem bronchus. (**b**) Relationship of LPA to trachea and esophagus. (**c**) Repair is by transecting LPA at its origin from RPA and anastomosing the LPA to the MPA at a site that approximates usual anatomic configuration. The tracheal stenosis has also been resected, and an end-to-end tracheal anastomosis is shown. (**d**) Postoperative relationship of neo-LPA to MPA anastomosis shows the relatively long distance from the original LPA takeoff from the RPA. *LPA* left pulmonary artery, *MPA* main pulmonary artery, *RPA* right pulmonary artery. (Reproduced with permission from: Backer CL, Mavroudis C. Vascular Rings and Pulmonary Artery Sling. In Mavroudis C, Backer CL [eds]: *Pediatric Cardiac Surgery*, 4th ed., 2013, Oxford, UK, Wiley-Blackwell, pp. 234–255)

eft pulmonary artery is then oversewn with r

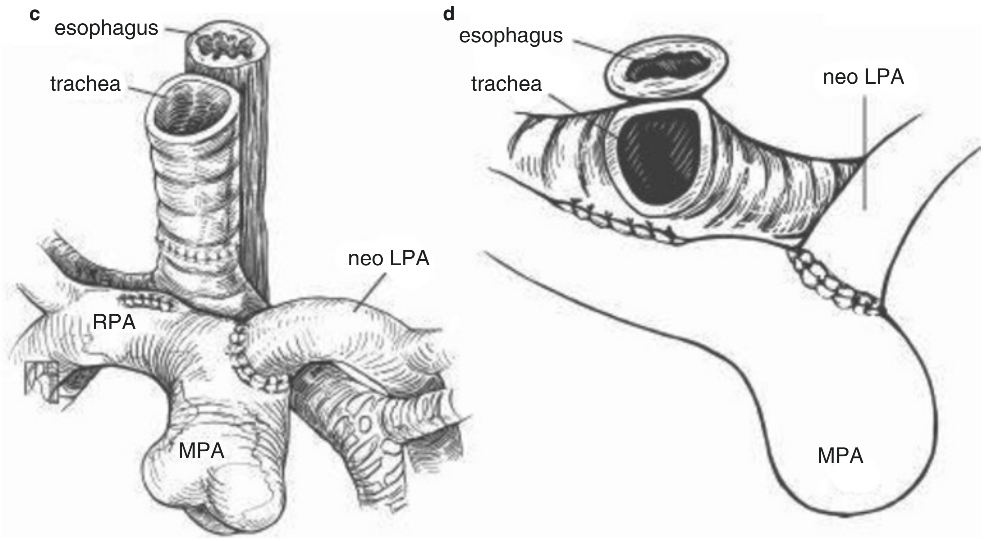

Fig. 108.6 (continued)

reimplantation into the main pulmonary artery is either at the site of the divided ligamentum or close to this. The left pulmonary artery is often excessively long and can either be shortened by removing a small segment or spatulated. A partial occlusion clamp is placed on the main pulmonary artery and a coronary punch is used to create an opening corresponding to the size of the left pulmonary artery. The left pulmonary artery is then anastomosed to this opening with running PDS suture. If there is an associated intracardiac anomaly it can be repaired at this time with the use of aortic cross-clamp. Finally, the associated tracheal stenosis, if present, is repaired with tracheal resection or slide tracheoplasty.

Since 1985, 40 patients have had pulmonary artery sling repair at our institution using median sternotomy with cardiopulmonary bypass. Median age was 0.2 years; 75% of the patients had tracheal stenosis secondary to complete cartilage tracheal rings. There were no early deaths or complications related to the use of cardiopulmonary bypass. The median hospital stay was 24 days. There have been two late deaths from late complications of tracheal surgery. All left pulmonary arteries are patent with mean percent flow by perfusion scan of 41% to the left lung, 59% to the right lung.

Slide Tracheoplasty

Our technique of slide tracheoplasty is to fully dissect the trachea and then find the midportion of the tracheal stenosis with intraoperative flexible fiberoptic bronchoscopy (Fig. 108.7a–c). The trachea is then transected in the midportion of the stenosis. Two longitudinal incisions are made in the superior and inferior portions of the transected trachea. The two portions of the trachea slide together and are sutured with a running PDS suture. We have now performed slide tracheoplasty in 27 patients with two operative mortalities. Cincinnati Children's Hospital reported 80 patients undergoing slide tracheoplasty with a 5% mortality [13]. Great Ormond Street reported 101 patients with a 12% mortality rate [14].

Rare Vascular Rings

Before all patients had CT or MRI there were a number of case presentations reporting rare vascular rings to heighten the awareness of surgeons who might have to make an intraoperative decision. These case reports focused on interpretation of barium swallows and chest radiographs for clues of these rare anomalies. In the current era all patients undergoing vascular ring surgery should have advanced cross-sectional imaging which will in nearly all instances prevent the need for intraoperative decision-making such as that performed by Potts when he did the first pulmonary artery sling repair.

One important type of rare vascular ring is the circumflex aorta. This is a rare vascular ring that occurs when a patient with a right aortic arch has the descending thoracic aorta crossing posteriorly from right-to-left *above* the level

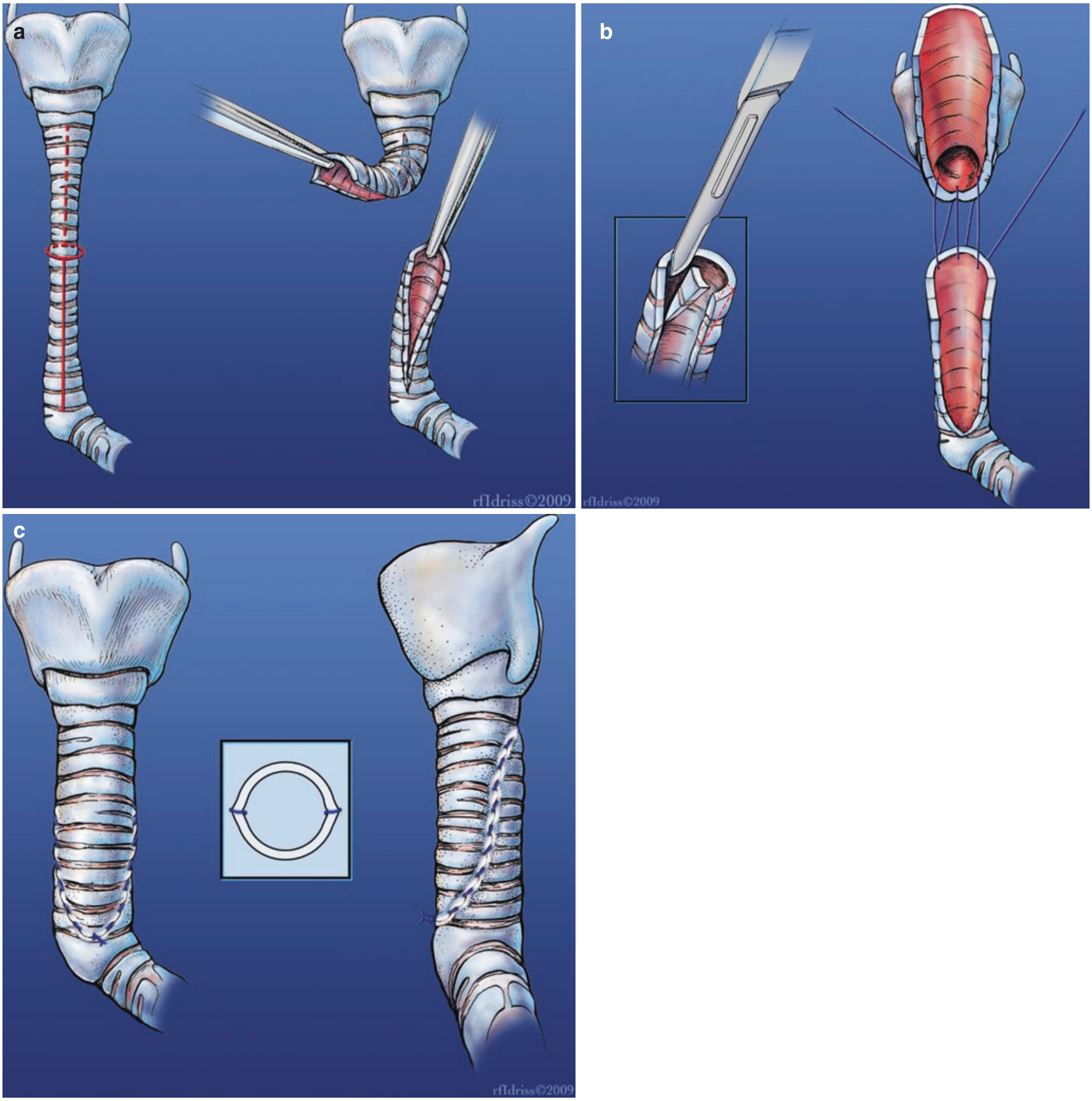

Fig. 108.7 (**a**) Slide tracheoplasty; absent right lung. The patient has been placed on cardiopulmonary bypass. The trachea is transected in the midportion of the tracheal stenosis. This site is determined by either external examination or by internal fiberoptic bronchoscopic findings. The inferior portion of the trachea is incised anteriorly and the superior portion of the trachea is incised posteriorly. (**b**) The ends of the trachea are beveled as shown in the small inset. The anastomosis is performed with running 6/0 polydioxanone suture. The suture line is started superiorly (parachute technique) and finished inferiorly just above the carina. (**c**) Completed slide tracheoplasty. The everting running suture line helps to avoid the "figure of 8" configuration problem after the completed repair. (Reproduced with permission from Backer CL et al. *Ann Thorac Surg* 2009;88:624–630)

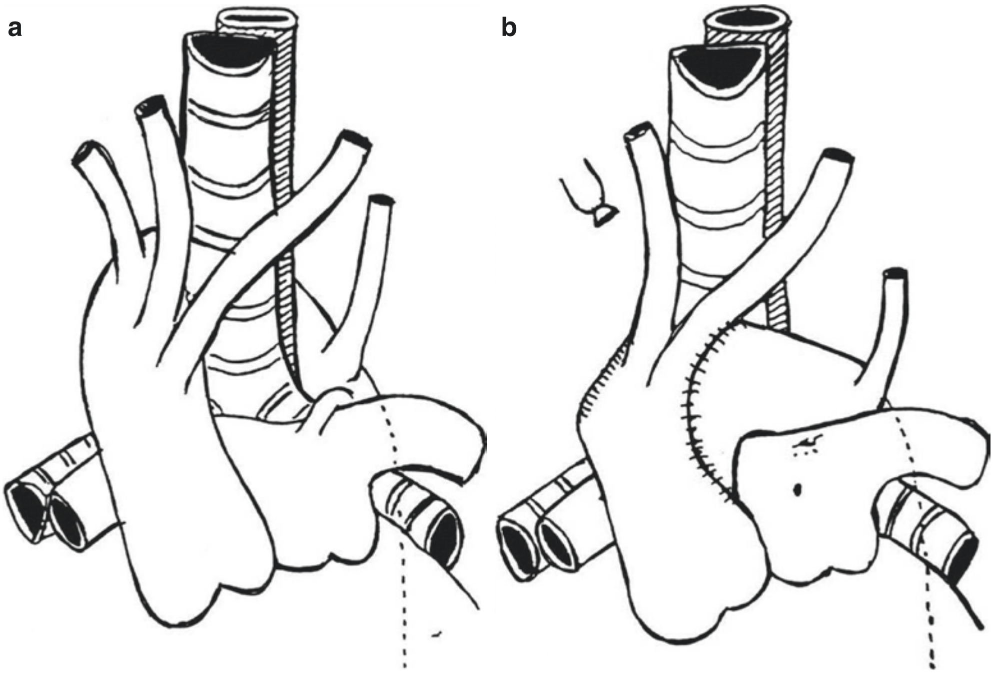

Fig. 108.8 The Uncrossing Procedure. (**a**) The vascular anatomy presents in circumflex aortas: the right-sided aortic arch passes over the right main bronchus, then takes a retroesophageal course and joins the left-sided descending aorta passing posterior to the trachea above the carina. (**b**) Schema of the aortic uncrossing procedure. The right subclavian artery is divided. The aorta arch is transected proximal to the origin of the right subclavian artery, mobilized, and reanastomosed to the left side of the ascending aorta and left carotid artery, in front of the trachea. In our series thus far we have preserved the subclavian artery connection to the aorta. (Reproduced with permission. Robotin MC, *J Thorac Cardiovasc Surg*. 1996;112:415–423)

of the carina. The trachea and esophagus are then not only encircled by the vascular ring but there is compression from the posterior limb of the right arch as it crosses from right to left. Although ligamentum division will divide the ring, it does not relieve the compression produced by this highly abnormal vascular anatomy. The operation that we have used to treat these patients is called the aortic uncrossing procedure which was first reported by Planché and Lacour-Gayet in 1984 [15]. The aortic uncrossing procedure is performed through a median sternotomy with the use of cardiopulmonary bypass, hypothermia, and a short period of circulatory arrest (Fig. 108.8a, b). The aorta is transected distal to the take-off of the right subclavian artery and the stump oversewn. The descending thoracic aorta is brought anterior to the trachea and esophagus and then anastomosed to the side of the ascending aorta. We have now performed the aortic uncrossing procedure successfully in eight patients [16]. Age of the patients ranged from 1.5 to 6 years of age.

Another rare vascular compression syndrome is where the left mainstem bronchus is compressed by a midline descending aorta. In 2016 McKenzie and colleagues described a novel surgical treatment consisting of division and translocation of the descending thoracic aorta to the proximal ascending aorta [17]. We have also performed this operation in a 4-month-old infant [18].

Conclusions

A diagnosis of a vascular ring requires a high index of suspicion by the clinician. Clues to this diagnosis are noisy breathing, a barky cough, recurrent upper respiratory tract infections, and dysphagia. The two most common true vascular rings are double aortic arch and right aortic arch with left ligamentum. Both are repaired through a thoracotomy with division of the ligamentum, division of the smaller of the two aortic arches for double aortic arch, and resection of a Kommerell diverticulum if present. Diverticulum resection frequently requires transfer of the left subclavian artery to the left carotid artery. Almost all patients have resolution of their symptoms over a period of 6 months to 1 year. Patients with a pulmonary artery sling often present because of the frequent association with tracheal stenosis from complete cartilaginous tracheal rings. These patients are diagnosed with CT imaging and repaired through a median sternotomy. With the use of cardiopulmonary bypass the left pulmonary artery is reimplanted in the main pulmonary artery in its normal anatomic position. Simultaneous repair of associated intracardiac lesions and slide tracheoplasty for congenital tracheal stenosis are performed. Care of vascular ring patients requires very close cooperation between multiple services including cardiothoracic surgery, otolaryngology, anesthesia, and critical care.

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Congenital Left Ventricular Outflow Tract Obstruction

109

Imran Saeed

High Yield Facts

- Subvalvar aortic stenosis (SAS) is a narrowing below the aortic valve.
- SAS can exist as discrete or tunnel-like forms.
- Surgery in SAS is indicated if mean gradient >30 mmHg (discrete stenosis), >50 mmHg (tunnel stenosis), or if symptoms or aortic regurgitation is present.
- Surgical options in SAS depend on associated abnormalities and include resection of the fibrous ridge, modified Konno and Ross-Konno procedure.
- Early mortality is low (<1%) for simpler forms of SAS and ~2% for more complex forms.
- Recurrence rates in SAS vary between 5% and 16% and may be reduced by additional septal myectomy.
- Supravalvar aortic stenosis (SVAS) is associated with deletions and mutations of the elastin gene and Williams syndrome.
- SVAV exists in hourglass, diaphragmatic and diffusely hypoplastic forms.
- Pulmonary artery and coronary artery stenoses can co-exist in SVAS.
- Biventricular hypertrophy and coronary abnormalities increase risk of sudden death in SVAS.
- Surgical indications for SVAS include peak gradient >40–50 mmHg, ≥mild aortic regurgitation, or evidence of coronary ischaemia.
- Surgical options for SVAS include single patch, inverted bifurcated Y-patch, three-patch and sliding aortoplasty or arch augmentation.
- Good early survival but higher long-term mortality compared to age-matched populations exists for SVAS.

Introduction

Congenital left ventricular outflow tract obstruction (LVOTO) can be defined as impedance to ejection from the left ventricle (LV). It is comprised of a group of relatively common anomalies that account for 3–10% of congenital heart disease [1].

Resistance to ejection occurs at one or more points between the LV and the ascending aorta and congenital LVOTO is categorised as [1]:

- Valvar (60–75%)
- Subvalvar (15–20%)
- Supravalvar (5–10%)

Congenital valvar aortic stenosis is discussed in detail in Chap. 101. Subvalvar (SAS) and supravalvar aortic stenosis (SVAS) are discussed separately below.

Subvalvar Aortic Stenosis

Overview

SAS is a narrowing that occurs below the aortic valve. It is a congenital condition but is rarely seen in infancy [2]. Certain anatomic substrates promote SAS (Table 109.1) and a four-stage aetiology based on these abnormalities can explain its development (Fig. 109.1) [3].

SAS can occur in isolation (<50% of cases) or in association with other congenital cardiac lesions. SAS also occurs as part of Shone's complex and can also be familial [4].

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Anatomy

SAS is classified with the following forms and subtypes [5]:

- Discrete (localised)
  - *Fibrous*
  - *Fibromuscular*
- Tunnel-type

There is continuum between the forms, and progression from discrete to tunnel-type SAS can occur [2].

- Discrete (localised) SAS
  - *Fibrous (also called 'membranous')*
    This is the commonest form. It usually manifests as a 2–3 mm thick circumferential or crescentic ridge a few millimetres below the cusps of the aortic valve. The ridge can also adhere to the base of the coronary cusps [5].
  - *Fibromuscular*
    If the fibrous ridge adheres to hypertrophied muscular ventricular septum (beneath the area of the right coronary cusp) the resulting stenosis is described as fibromuscular [5].
- Tunnel SAS
  Tunnel SAS is much less common than discrete SAS. The subaortic area is diffusely hypoplastic: circumferential fibrosis commencing at the aortic annulus extends downwards (1–3 cm) towards the LV apex. In its severest form the tunnel is long and the aortic annulus is small [5].

Table 109.1 Anatomical substrates for subaortic stenosis

Substrate	Note
Aortomitral separation with anterolateral muscle of Moulaert	*Normal aortic and mitral valve continuity is lost: often separated by 5–6 mm* *Muscle of Moulaert: muscle bundle between left coronary cusp and ALMV*
Steep aortoseptal angle	*Steeper angles elevate shear stress. The presence of a VSD enhances this effect*
Hypertrophied ventricular septum	
Anterior or posterior malalignment VSD	

Modified from [3, 4]
ALMV anterior leaflet mitral valve, *VSD* ventricular septal defect

Pathophysiology

As with other causes of LVOTO, SAS results in pressure overload with subsequent LV hypertrophy (LVH) of varying degrees. When sufficient this causes subendocardial ischaemia.

In addition, the aortic valve may become regurgitant because of [4]:

- Direct cusp impingement by the fibrous ridge
- Cusp thickening—secondary to the jet from the stenotic orifice
- Associated infective endocarditis

Presentation, Diagnosis and Indications for Surgery

Presentation is usually with an asymptomatic murmur. If the stenosis is severe, symptoms can include those of congestive cardiac failure, exertional dyspnoea, chest pain, and syncope. Sudden death is unusual.

Aortic regurgitation is present in up to two-thirds of patients. This is usually trivial or mild but can increase in severity, and ultimately require valve replacement [4]. Transthoracic echocardiography is usually sufficient for diagnosis.

The degree of obstruction is usually progressive. Surgery is considered above a mean gradient of 30 mmHg. Below this value, most children have quiescent disease and above this value LV gradient and aortic valve regurgitation progression is quicker [6].

Indications for surgery include:

- Symptoms
- Mean gradient >30 mmHg
- Aortic regurgitation (even if gradient mean <30 mmHg)
- Disease progression on imaging

A higher threshold (higher gradient or moderate to severe LVH) is used to indicate surgery for tunnel-type stenosis because of the more extensive surgery required to treat this sub-group [7].

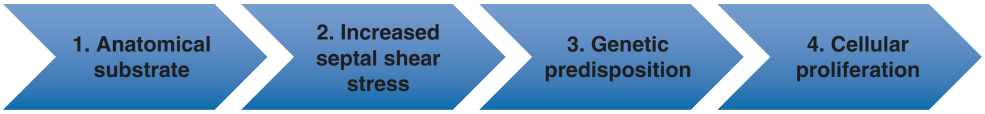
1. Anatomical substrate
2. Increased septal shear stress
3. Genetic predisposition
4. Cellular proliferation

Fig. 109.1 Four step model for the development of SAS. (Modified after [3])

Surgical Management

Surgery is the treatment of choice. For discrete SAS with a normal aortic valve and normal sized aortic annulus, surgical options include:

- Resection of the discrete fibrous shelf
- Modified Konno operation

For tunnel-type SAS or the presence of a small aortic annulus and aortic valve, surgical options include various forms of aortoventriculoplasty as well as the modified Konno operation:

- Aortoventriculoplasty procedures:
  - Ross-Konno
  - Konno
- Modified Konno

Resection of Fibrous Shelf

Key steps for this procedure are outlined in Table 109.2 and elements of the procedure are shown in Fig. 109.2a, b. Concomitant myectomy may reduce recurrence rates [8, 9]: a wedge of septal muscle is removed between the nadir of the right coronary and left coronary cusps (exercising caution with the depth of the incision to avoid creating a VSD). Similar caution is exercised in excising the fibrous shelf rightward of the nadir of the right coronary cusp to avoid heart block.

Table 109.2 Outline of steps for performing resection of discrete subaortic stenosis

- Median sternotomy
- High aortic and RA cannulation
- LV vent: right superior pulmonary vein
- Antegrade and direct ostial cardioplegia
- Hockey-stick incision into non-coronary sinus
- Suture suspension of commissures and under nadir of cusps to improve exposure
- Traction suture to adequately grip ridge
- Commence excision under nadir of right coronary cusp
  - Radial incision here to enter correct plane
- Start excision
  - Blunt and sharp dissection to excise circumferentially
- Carefully peel off aortic cusps if adherent
- Excise wedge of ventricular septal muscle leftward of nadir of right coronary cusp
- Close aortotomy
- Declamp after deairing
- Wean cardiopulmonary bypass
- Transoesophageal echocardiogram

LV left ventricle, *RA* right atrium

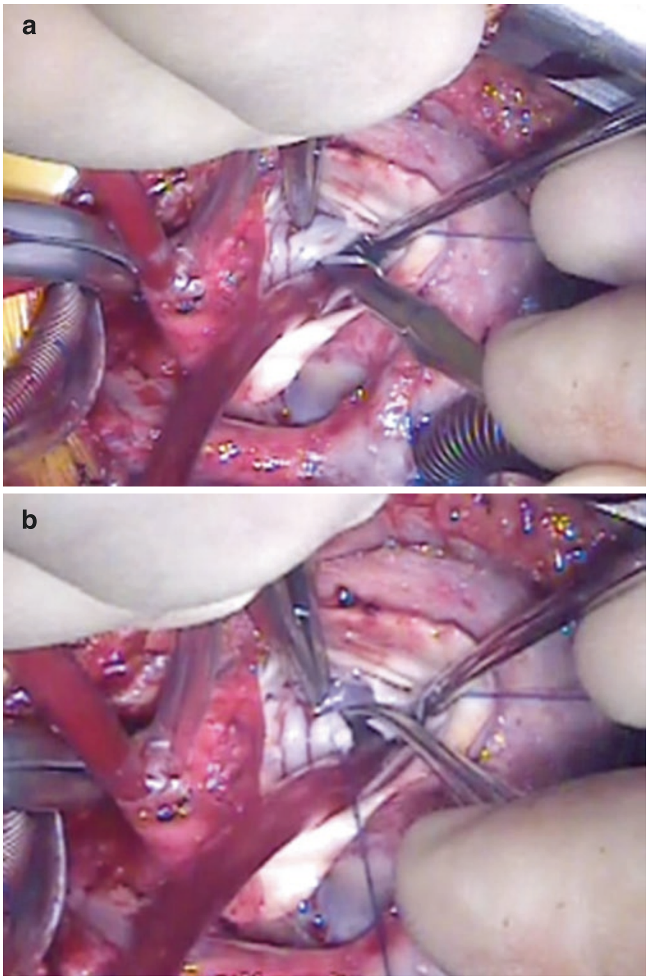

Fig. 109.2 Surgeon's view and resection of discrete fibrous SAS. (**a**) Sharp initial radial incision into the fibrous ridge allows entry into the correct plane (the starting point for this incision is the nadir of the right coronary cusp). (**b**) Subsequent blunt dissection using a Watson-Cheyne dissector to enucleate the above ridge. A traction suture through the edge of the ridge (as seen above) helps 'grip' the membrane and thereby also aids exposure. The plane between the fibrous ridge and underlying ventricular septal muscle can be clearly seen

Modified Konno Operation

Key steps for this procedure are outlined in Table 109.3. This technique can be useful for re-recurrence of discrete SAS as well as for tunnel-type stenosis (in the presence of a normal aortic valve and annulus) but carries a high risk of heart block.

Aortoventriculoplasty Procedures

The Konno incision, common to the eponymous operations listed, is an aortic root enlarging technique that enables anterior enlargement of the aortic annulus [10]: a longitudinal incision in the aorta is extended down to the annulus of the right coronary sinus just to the right of the commissure

Table 109.3 Outline of steps for performing resection a modified Konno operation for tunnel-type subaortic stenosis

- Median sternotomy
- High aortic and bicaval cannulation
- LV vent: right superior pulmonary vein
- Antegrade and direct ostial cardioplegia
- Hockey-stick incision into non-coronary sinus
- Transverse infundibular incision
- Right angled instrument passed through aortic valve to tent septal muscle
- Thickened septal muscle excised from RV and left side under aortic valve
  - Keep above muscle of Lancisi to avoid conduction tissue
  - Take care not to injure coronary cusps
- Resulting VSD closed with patch from RV
- Aortotomy and RV closed
- Declamp after deairing
- Wean cardiopulmonary bypass
- Transoesophageal echocardiogram

LV left ventricle, *RV* right ventricle, *VSD* ventricular septal defect

between the right and left coronary cusps (keeping well to the left of the orifice of the right coronary artery). This aortotomy is then extended through the right ventricular outflow tract (RVOT) via a transverse incision in the RV below the pulmonary valve [10]. The aortic annulus is divided between the right and left coronary cusps and the interventricular septum is incised for a variable length.

Konno Operation

After making the 'Konno incision' (described above) a diamond shaped patch is used to enlarge the incised ventricular septum, aortic annulus and root and a second patch is used to enlarge the opened RVOT to compensate for projection of the enlarged LVOT into the RVOT [5]. Once the inferior portion of the diamond shaped patch is sutured to the septal incision a prosthetic valve is inserted. The valve sutures are passed through the patch anteriorly (so the anterior portion of the 'annulus' is made of the inferior portion of the diamond shaped patch). The superior portion of this patch is then used to close the aorta above and the second patch used to close the RVOT [10].

Ross-Konno Procedure

The Konno operation as described above can be used along with the Ross operation. The pulmonary autograft in this case is harvested taking a tongue of RV free-wall muscle below the pulmonary valve portion, the length of which depends on the expected depth of the septal incision (ventriculoplasty) [11].

Outcomes

Surgery for SAS has generally good results. A large multicentre study from the United Kingdom reports 30-day mortality of 0.7% and 2.3% for what the authors define as simple and complex SAS respectively [12]. In this study, Konno-type procedures had a 2.4% 30-day mortality versus 1.5% where a Konno-type procedure was not required. Survival at 12 years was significantly better (statistically) for simple versus complex SAS at 98.8% and 96.1% respectively. Risk factors for long-term survival included: age <1 year at surgery and concomitant mitral valve disease [12].

Freedom from subaortic reintervention for simple SAS was 97.8% and 95.8% at 5 and 12 years respectively. In contrast, reintervention rates at the same time points for complex SAS were 88.8% and 83.7% respectively. Younger age at surgery, Shone's type complex and co-existing arch lesions predisposed to early recurrence [12]. These data are broadly in keeping with other publications.

Single centre studies suggest that septal myectomy at initial surgery for discrete SAS lowers recurrence rates (at 5 years of follow-up) compared to those in whom myectomy is not performed [8, 9].

Supravalvar Aortic Stenosis

Overview

Supravalvar aortic stenosis (SVAS) is an anomaly of the aortic root that is characterised by narrowing at the sinotubular junction (STJ). SVAS is associated with [13]:

- Williams-Beuren syndrome (up to 50%)
- Autosomal dominant familial disease (approximately 25%)
- Sporadic cases (approximately 25%)

Deletions and mutations of the elastin gene (chromosome 7q11.23) are the common link between these associations. This results in an elastin arteriopathy, whereby, the pulmonary arteries and other 'conducting' arteries can also be affected resulting in a generalised obstructive process involving both the systemic and pulmonary systems [14, 15].

Anatomy

SVAS occurs as the following variant forms [16] (Fig. 109.3):

- Hourglass
- Diaphragmatic or membranous
- Diffusely hypoplastic

The hourglass and membranous forms comprise localised stenoses confined to the STJ. These constitute the majority of lesions (82–86%) [17, 18]. The diffusely hypoplastic form is rarer and involves the entire ascending aorta and may extend as far as the descending aorta.

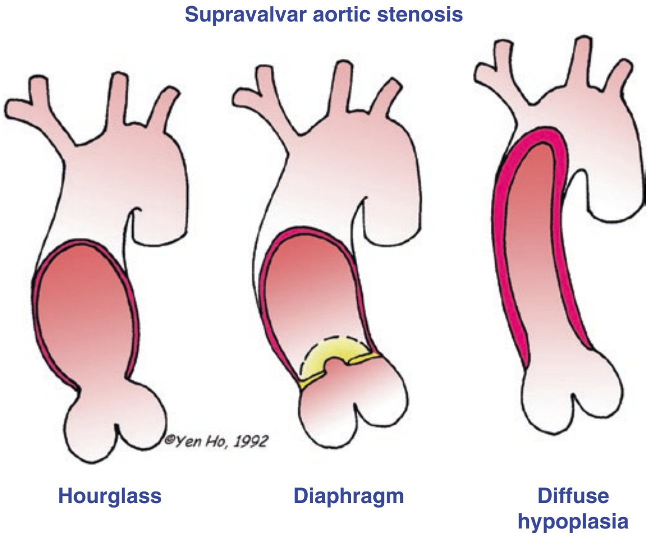

Fig. 109.3 Morphological subtypes of supravalvar aortic stenosis. (Drawing courtesy of Professor Siew Yen Ho, The Royal Brompton Hospital, London)

Scanty, defective elastic fibres and accumulation of excess collagen and smooth muscle within the vascular wall results in medial hypertrophy and dysplasia of the aortic wall, resulting in thickened and rigid vessels [13, 19].

Internally, the main feature is a thick intimal ridge at the STJ. The aortic valve leaflets are often thickened and their free edges can become adherent to this ridge and obstruct coronary blood flow [13]. In addition, the resultant high pressure in the aortic sinuses results in thickened, dilated and stenosed coronary arteries [20].

Other anatomical lesions associated with SVAS include [13, 20]:

- Bicuspid aortic valve (25–50%)
- Subaortic stenosis (15%)
- Coronary ostial stenosis
- Extramural coronary arteries that are: thickened and dilated and have diffuse stenoses
- Peripheral pulmonary artery stenosis (up to 80%)

It is also not uncommon for more central pulmonary artery stenoses to co-exist [19].

Pathophysiology

As with other forms of LVOT, SVAS results in LVH. In patients with severe pulmonary stenosis, high RV pressure and RV hypertrophy exists along with LVH.

The thickened and rigid aorta is less distensible, resulting in a widened pulse pressure and thus a reduction of diastolic phasic flow in the coronary arteries (loss of the Windkessel effect) [19].

Ultimately, there is both an increase in myocardial oxygen consumption and a decrease in myocardial oxygen supply. Biventricular hypertrophy predisposes to subendocardial ischaemia and this ‘supply-demand’ mismatch is further exacerbated by the mechanical restrictions to coronary blood flow previously discussed [19]. This results in a very high risk of sudden cardiac death compared to age-matched populations, as well as following procedural sedation or anaesthesia [19, 21].

Presentation and Diagnosis

The diagnosis of SVAS is usually established in the first year of life (neonatal presentation is rare) [22].

Symptoms may be absent even in the presence of significant stenosis but can include angina, exertional dyspnoea and syncope, and congestive cardiac failure [20]. Patients may have signs of Williams syndrome if this is present (Table 109.4).

There may be higher right upper limb (compared to left upper limb) pressures: the SVAS directs blood toward the right side of the aorta and innominate artery via a ‘Coanda effect’ (the affinity of a jet stream to adhere to a wall) [20].

Echocardiography is diagnostic and a pre-operative CT (without sedation) is useful as it allows evaluation of the entire aorta, proximal coronary arteries and pulmonary arteries [21].

Indications for Surgery

Indications for surgery include [7, 15]:

- Symptoms
- Peak gradient >40–50 mmHg
- Mild (or greater) aortic regurgitation
- Evidence of coronary ischaemia

SVAS gradients of less than 20 mmHg are stable over time and some cases of SVAS are seen to regress [17, 22]. SVAS is nevertheless, considered a progressive lesion, and significant LVH need not be present prior to proceeding with surgery [15]. Intermediate gradients (peak gradient <30–40 mmHg) can be followed-up closely if there is no LVH [7]. Pulmonary stenoses tend to improve with time.

Table 109.4 Features of Williams syndrome [20]

• Elfin facies
• Metal retardation
• Small stature
• Infantile hypercalcaemia
• Supravalvar aortic stenosis
• Pulmonary artery stenosis
• Renal abnormalities

Surgical Management

Surgery is the mainstay of treatment. Hourglass and membranous forms (localised SVAS) are managed similarly. The diffuse form requires different approaches.

Anaesthesia is administered with a view to minimising ischaemia [19]. The predisposition to cardiac arrest appears to be independent of the severity of SVAS and it is suggested that elective procedures for SVAS are undertaken in units where rapid-response ECMO is available should standard resuscitation measures fail [19]. The surgical team should be present at the induction of anaesthesia.

General principles of surgical management include [15]:

- Relieving the stenosis and restoring root geometry
- Avoidance of aortic regurgitation
- Management of associated lesions

Surgery for Localised SVAS

Surgery for SVAS usually involves patch augmentation of the sinuses of Valsalva [18]. Various repairs are described [23–26]:

- Single-patch (McGoon)
- Two-patch (inverted Y-shaped patch) (Doty)
- Three-patch (Brom)
- No patch: sliding aortoplasty [autologous three-sinus repair (Myers-Waldhausen)]

The former two repairs are also described as being 'non-symmetric' whilst the latter two repairs are 'symmetric' [18].

Surgery involves median sternotomy, right atrial cannulation, high aortic cannulation (close to the take-off of the innominate artery) and antegrade cardioplegia. Our preference is to use pulmonary homograft for patch repairs but other biomaterials can be used.

Single-Patch (McGoon) Technique

A longitudinal aortotomy is started above the STJ and extended down into the middle of the non-coronary sinus to a few millimetres above the annulus. The fibrous ridge is excised and the patch used to augment the aorta as distally as possible.

Two-Patch Repair (Inverted Y-Shaped) Doty Technique

The longitudinal incision is as for a single patch repair with an additional incision into the base of the right coronary sinus (well to the left of the orifice of the right coronary artery) forming what looks like an inverted-Y. An inverted pantaloon shaped patch is used to augment the sinuses and then the ascending aorta [15, 27]. Two separate elliptical patches can also be used, suturing them to each other anteriorly whilst keeping the non-coronary sinus patch longer to augment the distal ascending aorta [28].

Three-Patch (Brom) Technique

The aorta is transected just above the STJ. Vertical incisions are made into each of the sinuses of Valsalva and 'shield' shaped patches sutured into each sinus [21]. If the patches are too wide, commissural splaying can result in aortic valve regurgitation [15]. The width of the patches can be determined by dividing the circumferential augmentation required at the STJ by 3 [21]. The ascending aorta is also augmented anteriorly [15, 21].

Sliding Aortoplasty: Three-Sinus Repair (Myers-Waldhausen)

The aorta is transected and incisions made into the sinuses of Valsalva as in the Brom technique. Three complementary vertical incisions are made in the distal aorta out of phase with the proximal incisions. This allows interdigitation of proximal and distal flaps, the main advantage being the sole use of autologous tissue and, thereby, the prospect of growth potential [15, 27].

Surgery for Diffuse Supravalvar Aortic Stenosis

If diffuse hypoplasia is present, the aorta (including the transverse arch and beyond) may require patch augmentation using a continuous cerebral perfusion or circulatory arrest techniques.

Outcomes

Early results are generally good. A recent multicentre European study reports early mortality of 5% and surgical reoperation rates of 12.6% [29] whilst recent single centre studies report no early mortality [21, 30]. Some studies report no difference in outcome based on the surgical technique [18, 29] whilst others suggest that two and three-patch reconstructions result in lower mortality and reoperation rates and lower post-operative gradients [31, 32]. Diffuse hypoplasia, younger age, and concomitant pulmonary artery stenosis are risk factors for death following surgery [29, 30].

Longer-term follow-up suggests significant mortality compared to age-matched populations with 30 and 40-year survival of 81% and 68% respectively, hence, calls for intensification of follow-up following SVAS repair [18, 33].

Conclusion

Congenital obstruction of the LVOT remains a significant problem and multilevel obstruction can often coexist. Obstruction can take several morphological forms and may involve the subvalvar, valvar or supravalvar portion of the LVOT. Knowledge of the substrate of LVOTO, its physiopathology and natural history allows planning of the appropriate surgical repair and the postoperative management.

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Pediatric Heart Transplantation

110

James K. Kirklin

High Yield Facts

- More than 700 pediatric heart transplants are performed annually.
- Average survival of pediatric heart transplants exceeds 90% at 1 year and, among infants, the median survival is more than 20 years.
- Major causes of death include graft failure, allograft vasculopathy, rejection, infection, and malignancy.
- With current preservation techniques, the incidence of early graft failure has been reduced to about 2%.
- About 40% of patients experience one or more rejection episodes in the first year.
- Antibody mediated rejection is much less common but when associated with hemodynamic compromise 50% of patients die within 5 years.
- Infection incidence is time-related, with bacterial infections most prevalent in the first 2 months.
- Post-transplant lymphoproliferative disease is caused by Epstein-Barr virus in over 80% of cases, and the greatest risk is between 6 and 12 months.
- Allograft vasculopathy, a manifestation of chronic rejection, affects 15% of patients by 5 years and 30% by 10 years.
- Allograft vasculopathy is the most common indication for retransplantation with expected graft survival only slightly worse than with the original graft.

Introduction and Historical Note

The historical roots of pediatric heart transplantation date back to the earliest days of clinical heart transplantation, when Adrian Kantrowitz performed the world's second human heart transplant. Three days after Barnard's historic first human heart transplant (December 3, 1967), Kantrowitz transplanted an 18 day old infant with Ebstein's malformation [1]. Unfortunately, the baby died several hours after the transplant from acute graft failure. Many other successful pediatric heart transplants would follow. Leonard Bailey is considered the father of infant heart transplantation for his landmark pediatric heart transplant program at Loma Linda, beginning with the unsuccessful (and only) attempt at infant xenotransplantation with the Baby Fae baboon to human heart transplant in October of 1984.

Currently, about 700 pediatric heart transplants are performed annually worldwide [2]. Congenital heart disease accounts for approximately 40% of pediatric heart transplants. Among infants, more than half of transplants are for congenital heart disease, but the frequency of that diagnosis decreases to about 25% among teenagers (Fig. 110.1) [2].

Indications for Pediatric Heart Transplantation

Cardiomyopathy

Dilated cardiomyopathy accounts for 75% of pediatric patients undergoing transplantation for cardiomyopathy, of which 20% are *familial*, most commonly autosomal dominant.

Anthracycline-induced cardiomyopathy accounts for a small minority of transplants for cardiomyopathy. Anthracycline compounds are used in the treatment of certain leukemias and solid organ tumors of childhood. The major predictor of subsequent heart failure is the cumulative anthracycline dose, likely related to oxygen free radical formation

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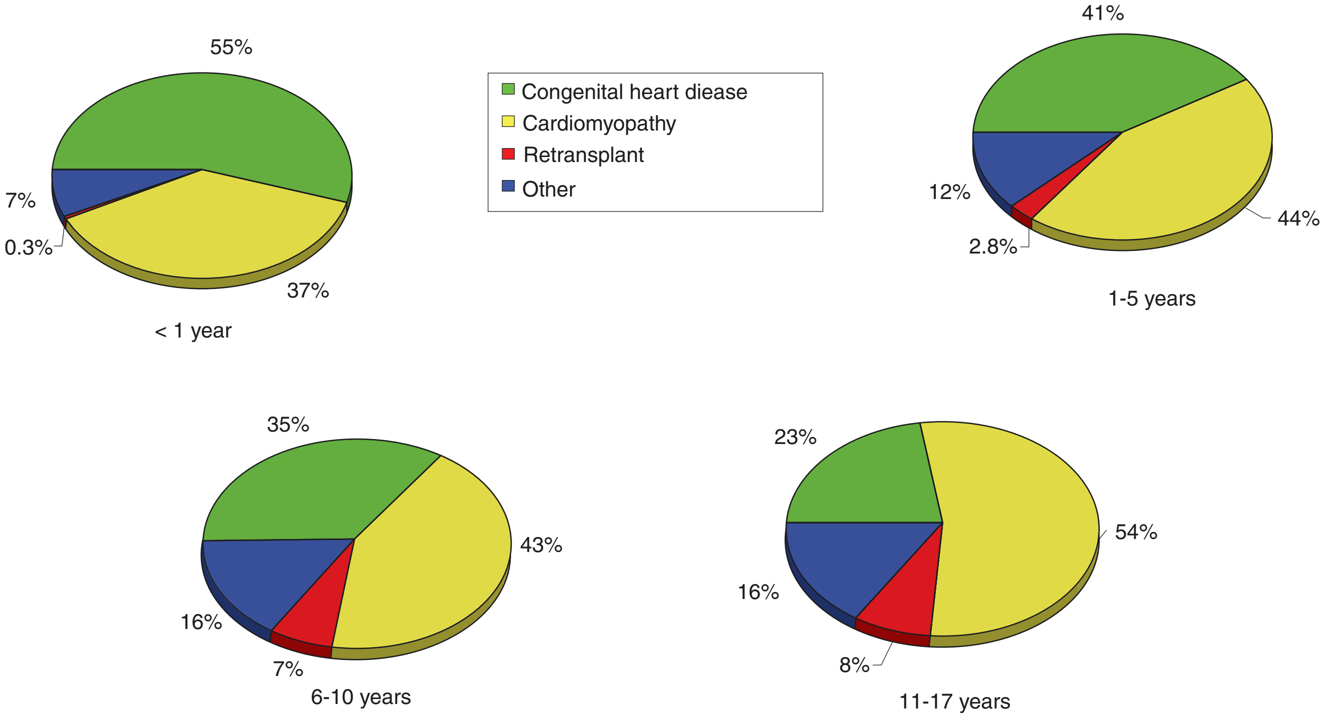

Fig. 110.1 Recipient diagnosis by age for transplants completed from 2009 to June 2016. (Reproduced with permission from Rossano et al. [2])

and other mechanisms which can induce cardiac myocyte apoptosis [3]. Onset of heart failure symptoms typically occurs within the first year, but may be delayed for 5 years or more. At present, the only effective therapy for end-stage anthracycline cardiomyopathy is transplantation.

Hypertrophic cardiomyopathy (HCM) (about 5% of transplants for cardiomyopathy) is characterized by inappropriate left ventricular hypertrophy with preserved systolic function, with or without left ventricular outflow obstruction. The histologic picture consists of myocardial fiber disarray. HCM, with an estimated incidence of 2 per 1000, is the most common cardiac cause of sudden death in teenagers and young adults [4].

Restrictive cardiomyopathy is a rare cause of childhood cardiomyopathy, but is the second most common cardiomyopathy (after DCM) among pediatric transplant recipients, accounting for 10–12% of cardiomyopathy transplants. The associated diastolic dysfunction results in severe biatrial enlargement with marked elevation of atrial pressures [5].

Congenital Heart Disease

Two-ventricle pathway: Patients with potentially correctable congenital heart disease who are at greatly increased operative risk for repair can be considered for cardiac transplantation. Differences in experience and surgical results compared to transplantation influence the decision regarding cardiac transplantation versus attempted surgical correction in certain malformations such as complex truncus arteriosus (with severe truncal valve insufficiency, interrupted aortic arch, or coronary artery anomalies), some severe forms of Shone's syndrome, and certain other malformations. Progressive ventricular failure from a multitude of etiologies can present following two-ventricle repairs. When heart failure is poorly responsive to medical therapy, and when further operations are considered not advisable, cardiac transplantation can be considered.

Single ventricle pathway: If two-ventricle repair is considered not possible or at greatly increased risk, a staged approach for the Fontan pathway usually includes three stages, culminating in the Fontan operation. When depressed ventricular function, particularly with associated systemic atrioventricular valve regurgitation, makes the Fontan operation unlikely to succeed, such patients may be considered for transplantation. When the Fontan procedure has been performed, failure can result from systolic or diastolic ventricular dysfunction or from "failing Fontan physiology", in which pulmonary vascular resistance is sufficiently elevated that right sided failure (since there is no pump on the right side) results. In these instances, patients can be considered

Table 110.1 General indications for heart transplantation in patients with congenital heart disease

1. Advanced symptomatic heart failure refractory to medical therapy and unlikely to benefit from surgical therapy or other invasive interventions
2. Life-threatening arrhythmias refractory to all available therapies
3. Presence of severe pulmonary hypertension with important risk of developing future fixed elevation of pulmonary vascular resistance to a level that would substantially increase the risk of orthotopic heart transplantation
4. Advanced heart failure with systemic ventricular dysfunction after prior repair or palliation that is associated with heart failure related growth failure and/or marked reduction in life expectancy and quality of life
5. One or more of the following anatomic or physiologic conditions not amenable to surgical intervention, even with preserved ventricular function:
(a) Severe stenosis (stenosis) or atresia in a proximal coronary artery
(b) Symptomatic severe insufficiency of a systemic atrioventricular valve in the setting of single ventricle
(c) Symptomatic arterial oxygen saturation (cyanosis) from a cardiac cause that is not considered amendable to surgical correction
6. Progressive right-sided heart failure following the Fontan procedure (failing Fontan) not responsive to medical or additional surgical therapies

for cardiac transplantation. The general indications for cardiac transplantation in congenital heart transplantation are listed in Table 110.1 [6].

Cardiac Tumors

Unresectable cardiac tumors represent a rare indication for cardiac transplantation, accounting for <1% of pediatric heart transplants. Since primary cardiac tumors rarely metastasize, cardiac transplantation may be advised if the tumor is confined to the portion of the heart removed at transplantation. The most common tumor of infancy and childhood is rhabdomyoma, often with associated tuberous sclerosis. When spontaneous tumor regression is considered unlikely, heart transplantation may be indicated when there is severe left ventricular outflow obstruction, hemodynamic compromise, or serious ventricular arrhythmias [7].

Recipient Evaluation

Each potential recipient must undergo an evaluation which examines potential anatomic and physiologic derangements as well as other organ system dysfunction, systemic illness, and social factors which may preclude transplantation as a therapeutic option [8]. A typical evaluation protocol for pediatric patients is provided in Table 110.2 [8]. The general contraindications to pediatric heart transplantation are listed in Table 110.3.

Table 110.2 Pediatric cardiac transplantation evaluation protocol[a]

Cardiology	Chest X-ray ECG Echocardiogram Exercise stress test including maximal oxygen consumption[b] May include endomyocardial biopsy[c] May include drug studies to manipulate cardiac index and pulmonary vascular resistance
Hematology	Complete blood count and differential Prothrombin and partial thromboplastin time
Blood chemistry	Serum electrolytes, magnesium, calcium, phosphorus, transaminases, bilirubin, albumin, total protein, alkaline phosphatase, cholesterol, triglycerides, uric acid, lactic dehydrogenase, creatinine phosphokinase, carnitine
Renal	Urinalysis Serum blood urea nitrogen and creatinine 24-h urine collection for creatinine clearance[c]
Pulmonary	Pulmonary function tests[b]
Serology	Serologic, polymerase chain reaction, and/or nuclear acid amplification testing for CMV, EBV, varicella, herpes, hepatitis, HIV
Cultures	Blood, throat, urine, stool, sputum for bacterial viral, parasites, fungus[c]
Immunology	HLA typing Panel reactive antibody (titer and type of anti-HLA antibodies)
Neurology	CT or MRI scan[c] EEG[c]
Consultations	Neurology (also to exclude associated skeletal muscle disease)[c] Genetic[c] Psychology[c] Physical/Occupational therapy[c] Dietetics[c] Social worker Financial/health insurance coordinator

ECG electrocardiogram, *CMV* cytomegalovirus, *EBV* Epstein-Barr virus, *HIV* human immunodeficiency virus, *HLA* human leukocyte antigen, *CT* computerized tomography, *MRI* magnetic resonance imaging, *EEG* electroencephaglogram

[a] Modified from Ref. [8]. Canter CE: Preoperative assessment and management of pediatric heart transplantation. Proc Pediatr Cardiol 2000;11:91–97

[b] When feasible

[c] If medically indicated

Table 110.3 Contraindications to pediatric heart transplantation

• Irreversible elevated pulmonary vascular resistance (>6 WU m^2)
• Diffuse hypoplasia of right and left pulmonary arteries
• Total anomalous pulmonary venous connection without pulmonary venous confluence
• Ectopia cordis
• Active systemic infection
• Infection with HIV or chronic active hepatitis B or C
• Malignancy without cure or of recent onset
• Severe primary renal or hepatic dysfunction (unless concomitant kidney or liver transplant is planned)
• Multiorgan system failure
• Major central nervous system abnormality or injury
• Severe dysmorphism
• Marked prematurity (<36 weeks)
• Low birth weight (<2 kg)
• Positive drug screen
• Lack of family support

Anatomic Considerations

A major anatomic contraindication is small, diffusely hypoplastic, or stenotic pulmonary arteries (extending into and beyond the hilum) which cannot be satisfactorily enlarged surgically with patching or augmentation with donor pulmonary artery. Other anatomic features which would preclude safe cardiac transplantation include subsets of anomalous pulmonary venous connection without a suitable pulmonary venous confluence for direct anastomosis to the donor left atrium (unless they connect directly to the coronary sinus or right atrium), pulmonary vein obstruction which is not surgically correctable, and ectopia cordis. Abnormalities of body situs, systemic venous return, and malpositions of the great vessels can be managed surgically at the time of cardiac transplantation.

Pulmonary Vascular Resistance

The relationship between calculated PVR and the likelihood of acute post-transplant right ventricular failure and death remains controversial. Perhaps the most important factor is *reactivity* of the pulmonary vascular bed in response to lowering of the left atrial (or pulmonary capillary wedge) pressure and/or to the administration of pulmonary vasodilator agents. Patients with poor left ventricular function and left atrial hypertension may have a dramatic fall in pulmonary vascular resistance following periods of inotropic support and intensive heart failure management. A fixed resistance of >6 WU m^2, a pulmonary artery systolic pressure exceeding about 55 mmHg in the presence of left atrial pressure less than or equal to 20 mmHg, or a transpulmonary gradient (mean pulmonary artery pressure–pulmonary capillary wedge pressure) >15 all indicate a major increase in the risk of acute donor right heart failure early after the transplant.

When considering transplantation in neonates and small infants in the first few months of life, if the main and branch pulmonary arteries are normal in size and distribution, the elevated pulmonary vascular resistance of the newborn period usually rapidly normalizes after transplantation and is not associated with an increased risk of right ventricular failure. An important exception may be persistence of pulmonary venous obstruction (anomalous pulmonary venous connection with unrecognized obstruction, congenital pulmonary vein stenosis, or hypoplastic left heart syndrome with a restrictive atrial septal defect) for weeks or months while awaiting cardiac transplantation, which may induce marked elevation of pulmonary artery pressure that may not normalize promptly after cardiac transplantation.

The Sensitized Patient

The development of circulating antibodies directed against human leukocyte antigens (HLA) remains an important barrier to heart transplantation, particularly in the presence of previous cardiac operations, multiple blood transfusions, or the use of homograft patch material in prior reconstructions [9]. Controversy exists regarding the importance of specific values of preformed or "panel-reactive" antibodies (PRA) in predicting the likelihood of accelerated or hyperacute rejection. The detection of antibodies that fix complement by C1q single antigen beads is more reliable in identifying antibodies that are specific for the graft [10]. For sensitized patients, most centers currently rely mainly on virtual cross matches, in which the known anti-HLA antibodies of the recipient are compared with the HLA profile of the donor, without performing an actual prospective cross match. When patients are highly sensitized, therapies can be initiated to reduce the antibody titers. Most commonly used therapies include intravenous immunoglobulin, rituximab (a monoclonal antibody against B-cells), bortezomib (a protease inhibitor against plasma cells), and intermittent plasmapheresis (to reduce antibody titers). Success with these agents is mixed.

The Pediatric Heart Donor

The general contraindications to pediatric heart donation are (1) complex cardiac malformation, (2) overwhelming untreated sepsis, (3) suspected hepatitis or retrovirus infection, (4) positive serology or nucleic acid amplification testing for human immunodeficiency virus (HIV) or hepatitis C, and (5) marked reduction in myocardial contractility (fractional shortening less than 20% and/or major wall motion abnormalities) despite appropriate volume loading and inotropic support. Donor heart preservation has improved over the past decade, with a current incidence of graft failure by 30 days of about 2% [11].

The Transplant Operation

Heart transplantation for primary cardiomyopathy follows the same general construct as in the adult. However, in the setting of complex congenital heart disease, detailed planning is required for necessary reconstructions during implant. Five categories of anatomic abnormalities must be considered: (1) aortic arch hypoplasia or interruption, (2) anomalies of systemic venous return, (3) anomalies of pulmonary venous connection, (4) congenital or acquired stenoses or interruption of the central pulmonary arteries, and (5) cardiac situs anomalies. These reconstructions often require an additional length of anatomic segments in the donor [12].

Because of the frequent need for major pulmonary artery reconstruction, particularly following the Fontan procedure, some centers restrict donor selection to those in whom lung transplantation is not planned. This additional restriction can be avoided by routinely using thin bovine pericardium for reconstruction of the pulmonary arteries instead of donor pulmonary artery tissue [12]. Furthermore, this allows the donor heart to be kept cold in the storage container while all reconstructions are being carried out. The implantation process can then begin promptly when the heart is removed from the storage container. Overall, approximately one-third of patients with congenital heart disease, who undergo transplantation, will require additional surgical procedures at the time of transplant [13].

In the presence of extensive venous or arterial collateralization, endovascular coiling in the catheterization laboratory prior to transplantation should be considered, unless systemic oxygen saturation levels are marginal (in which case closure of remaining collaterals should be considered following cardiac transplantation). This carries an important advantage of decreasing pulmonary venous return during cardiopulmonary bypass and potentially improving cerebral perfusion (with reduced run off through aortopulmonary collaterals).

Since peripheral cannulation for cardiopulmonary bypass may be necessary in the event of bleeding at sternotomy or unusually difficult dissection, the patency of femoral vessels, subclavian arteries, carotid arteries, and internal jugular veins should be documented with ultrasound or angiography at the time of listing. Such documentation is also critical to ensure patent venous channels for subsequent endomyocardial biopsies.

Immunosuppression

Pre-transplant Immunosuppression

Pre-implant immunotherapy includes steroids, an antiproliferative agent, and usually a calcineurin inhibitor (unless renal function is compromised). Methylprednisolone is administered usually at a dose of 15 mg/kg up to a maximum of 500 mg intravenously on call to the operation room, then 10 mg/kg after discontinuation of cardiopulmonary bypass. Perioperative steroids are continued with intravenous methylprednisolone every 8 h for three doses.

Some type of “induction” therapy is employed in about 65% of pediatric heart transplant centers [11]. Antithymocyte globulin is used as induction therapy in about 45% of recipients, and interleukin-2 receptor (IL-2) antagonists (most commonly basiliximab, a chimeric mouse-human monoclonal antibody which acts as an IL-2 receptor antagonist) are used in just over 20%.

Maintenance Immunosuppression

Steroids: Controversy exists regarding the dose and duration of steroids as part of the maintenance immunosuppression protocol. Most programs initiate low dose oral prednisolone (dose varies among programs) early post-transplant with plans to taper off by 2–6 months. Sixty percent of pediatric recipients remain on prednisone during the first year, which decreases to 35% by year 5 [11].

Calcineurin Inhibitor: The vast majority of maintenance regimens include a calcineurin inhibitor. The two agents currently available are cyclosporine and tacrolimus. The use of tacrolimus, particularly when combined with mycophenolate, reduces the proportion of patients experiencing acute rejection during the first year compared to cyclosporine-based immunosuppression [11].

Complications of Heart Transplantation

Allograft Rejection

Acute Cellular Rejection

Endomyocardial biopsy (EMB) is considered the “gold standard” for diagnosis of cellular rejection and has a low rate of complications [14, 15]. The most important long-term complication of repeated EMBs is injury to the tricuspid valve support apparatus, resulting in severe tricuspid regurgitation (TR). Chronic severe TR may contribute to graft dysfunction and require tricuspid valve replacement with a tissue valve [16]. Rarely, acute massive TR early post-transplant resulting from iatrogenic chordal injury may be successfully treated with valve repair using expanded polytetrafluoroethylene artificial chords [17]. Particularly in small infants with limited venous access available for passing the bioptome, echocardiography is a useful adjunct for rejection surveillance, but it lacks the sensitivity to reliably detect asymptomatic refection [18, 19]. Gene expression profile testing may be useful for surveillance in patients who are older and at low risk for rejection [20]. B-type natriuretic peptide concentration may provide useful information about the allograft response to rejection [21].

Antibody-Mediated Rejection

Antibody-mediated rejection (AMR) involves deposition of antigen-antibody complexes along the vascular endothelial surface of the transplanted heart. Evaluation for AMR includes both EMB and examination of peripheral blood for circulating donor-specific anti-HLA antibodies. Histologic evidence for AMR on EMB includes endothelial “activation” with intravascular macrophages and capillary destruction.

Immunopathologic evidence includes positive immunofluorescence staining for CD4 deposition and positive immunoperoxidase studies for CD68-positive macrophages [22]. Rejection with hemodynamic compromise (HC) (reduced systolic function, occasionally with low cardiac output) is more likely with AMR than cellular rejection [23].

Treatment of Acute Rejection

Acute cellular ejection episodes are generally treated with pulse steroid therapy, either orally or intravenously for 3 days. Persistent or recurrent rejection episodes may require addition of anti-thymocyte globulin. When HC accompanies rejection, prompt inotropic support is recommended plus plasmapheresis (to remove cytokines and preformed antibodies). Treatment of AMR with HC also may include intravenous immunoglobulin to block antibody formation, administration of monoclonal antibodies against CD20 on B cells (rituximab), and in refractory cases, plasma cell destruction with a proteasome inhibitor targeting plasma cells (bortezimab) [24]. Once the patient is stabilized, long-term outcomes may be improved with the addition of photopheresis [25], which likely induces immunomodulation and destruction of anti-donor cytotoxic T cells [26, 27].

Outcomes

With current immunosuppression protocols, about 40% of patients experience one or more rejection episodes within the first year [28]. When rejection is associated with HC, subsequent survival is reduced (50% at 5 years) [28]. Risk factors for earlier onset of rejection include pre-transplant sensitization and older recipient age [11, 28].

Infection

Patients undergoing heart transplantation, with the obligatory immunosuppression, are at increased risk for a multitude of infections, particularly opportunistic infection. Most initial medical regimens include prophylaxis against pneumocystis carinii with trimethoprim/sulfamethoxazole, cytomegalovirus with ganciclovir, and candida with nystatin.

About 40% of patients suffer one or more serious infections within the first year [28]. The time-related risk profile varies for each type of infection, with the risk of bacterial and fungal infection highest early after transplant, while viral infection risk peaks at about 2 months [29]. Overall, about 50% of post-transplant infections are bacterial, 35% viral, 10% fungal, and <5% protozoal [30]. In the early transplant period (first month), *Staphylococci*, *Enterobacter*, and *Pseudomonas* are the most common organisms [31, 32]. Cytomegalovirus accounts for the majority of viral infections and overall is the most common infectious agent. Respiratory infection with respiratory syncytial virus is most common in children less than 6 months of age, with the potential long-term sequelae of significant reactive airway disease.

Malignancy

The most common malignancy after pediatric heart transplantation is post-transplant lymphoproliferative disease (PTLD). The greatest risk for PTLD is between 6 and 12 months post-transplant, but a low ongoing risk continues indefinitely. The cumulative risk of malignancy is about 10% by 10 years [11, 28].

Epstein-Barr virus (EBV) is the causative agent in over 80% of cases. EBV infection is usually accompanied by the conversion of a negative EBV serology before transplant to a positive serology post-transplant, most commonly in the setting of an EBV-negative recipient receiving an organ from an EBV-positive donor. EBV genome can usually be recovered from the tumor. About half of PTLD cases present with localized disease in the tonsils and adenoids, with a histologic diagnosis of plasmacytic hyperplasia [33]. Removal of tonsils and adenoids along with reduction of immunosuppression is usually curative.

The more serious forms of PTLD may involve one or multiple organ systems, including gastrointestinal, pulmonary, and central nervous system. The causative B-cell lymphoma can be either monoclonal or polyclonal. The first line of therapy includes reduction of immunosuppression, usually with reduction or elimination of the anti-proliferative agent and a reduced dose of the calcineurin inhibitor. Treatment of Isolated disease often includes surgical extirpation when feasible. Chemotherapy is standard. Close graft surveillance is necessary following completion of chemotherapy, since rebound rejection (in the setting of reduced overall immunosuppression) is common.

Allograft Vasculopathy

Transplant coronary allograft vasculopathy (CAV) is likely caused by intimal proliferation in response to antibody mediated rejection targeting the coronary endothelium. The diagnosis of CAV in the pediatric population has relied primarily on selective coronary angiography. More frequent rejection during the first 6 months after transplantation [34] and rejection with HC after the first year [34] have been identified as predictors of subsequent CAV. The incidence of CAV (based on angiography) is 15% at 5 years and nearly 30% by 10 years [35]. Survival after the first detection of CAV is about 50% at 5 years [28, 36].

Survival

Survival after pediatric heart transplantation has progressively improved over the past 30 years, and currently exceeds 90% at 1 year, 80% at 5 years and 65% at 10 years (Fig. 110.2) [37]. Available data indicates that median survival exceeds 20 years among infants, 18 years for children 1–5 years, 14 years for ages 6–10, and nearly 13 years for ages 11–17 years. The major cause of death during the first 10 years is graft failure, followed by allograft vasculopathy, rejection, infection, and malignancy (Fig. 110.3) [11].

Congenital heart disease has been consistently identified as a risk factor for mortality [37]. The results of transplantation for the failing single ventricle have progressively improved and now approach the late outcomes for other conditions. Other significant risk factors include ECMO support of at transplant, retransplantation, history of dialysis, renal dysfunction, ventilator at transplant, liver dysfunction, and sensitization [11].

Retransplantation

Given that the median graft survival among pediatric patients ranges from 10 to 20 years, an increasing number of patients are considered for retransplantation. The most common indication is CAV, followed by non-specific late graft failure [28]. Survival after retransplantation is somewhat worse than after primary transplant [11] and is less good if retransplantation occurs within the first year. Worst outcomes occur if the indication is early graft failure or acute rejection [28].

Future Directions

Pediatric heart transplantation has provided hope for thousands of children dying from advanced heart failure. Many have essentially a normal quality of life for 20 years or more. However, given the palliative nature of the procedure and the limited donor pool, other circulatory support

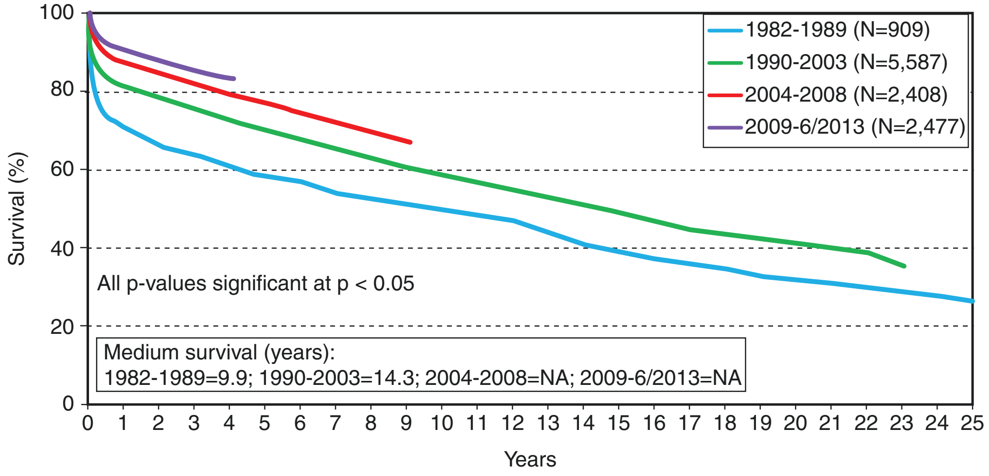

Fig. 110.2 Kaplan–Meier survival by era (Transplants: January 1982 to June 2013). (Reproduced with permission from Dipchand et al. [11])

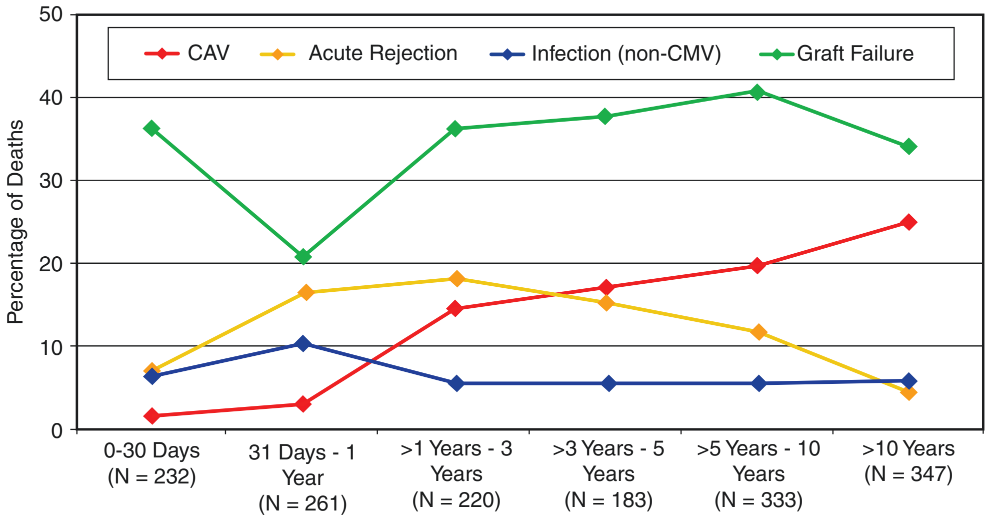

Fig. 110.3 Relative incidence of leading causes of death (Deaths: January 2004 to June 2014). (Reproduced with permission from Dipchand et al. [11])

systems are needed. In the coming 5 years, expect greater availability of small continuous flow mechanical circulatory support devices and the emergence of xenotransplantation, first in kidney transplantation (next 2 years) followed by infant hearts (5–10 years) [38].

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Review Questions

Choose the single BEST option.

1. **In the Arterial Revascularization Trial (ART), patients were randomly assigned to receive either bilateral internal thoracic artery grafts or a standard single left internal thoracic artery graft during coronary artery bypass grafting. The intention-to-treat analysis at 10 years follow-up reported**
   A. significantly improved all-cause mortality in the bilateral internal thoracic artery grafts group.
   B. significant between-group difference in the rate of repeat revascularization.
   C. no significant differences between the two groups for the composite outcomes of death from any cause, myocardial infarction, or stroke.
   D. significant between-group differences in cardiac mortality.
   E. significant between-group differences in stroke rate.
2. **A 60-year-old otherwise healthy man underwent successful aortic valve replacement for severe aortic stenosis with mild insufficiency. Preoperative angiogram showed minimal coronary disease. During the operation initial arrest was with cold antegrade cardioplegia though an aortic cannula, and maintenance was with intermittent cold retrograde cardioplegia. A left ventricular vent was used. Several hours postop as he was waking up there were multiple witnessed grand mal seizures and hemodynamic evidence of right ventricular dysfunction with several episodes of nonsustained ventricular tachycardia.**

   The most appropriate management is
   A. Hundred percent oxygen, induced hypertension and hyperdynamic condition, and avoidance of hyperthermia.
   B. Emergent cardiac catheterization and possible percutaneous interventions.
   C. Hyperbaric therapy with 50% oxygen and 50% nitrogen at a pressure of 3 atm.
   D. Immediate reoperation to place multiple coronary artery grafts with saphenous vein segments.
   E. IV anticonvulsant therapy, emergent CT scan of the chest and neurosurgical consultation.
3. **A 45-year-old man was referred for surgical evaluation after a 4.6 cm ascending aortic aneurysm was found. Cardiac catheterization demonstrated no significant coronary artery disease. He has a murmur heard best in the right second interspace and echo showed a bicuspid aortic valve with a valve area of 0.9 cm^2. With respect to the patient's care, which of the following statements is true?**
   A. Aortic pathology is anticipated to show increased fibrillin 1 content and decreased matrix metalloproteinase 2 activity.
   B. Aortic valve replacement alone is the appropriate recommendation for this patient.
   C. A Bentall procedure should be performed if the aortic root is dilated.
   D. Expectant followup of this patient is expected to show an aortic dilation rate equivalent to patients with tricuspid aortic valves.
   E. Reduction aortoplasty and supracoronary tube grafting (in addition to AVR) yield comparable long-term results.
4. **One week ago a 40-year-old man patient on chronic hemodialysis underwent AVR with a mechanical valve for calcific aortic stenosis. Preoperative ventricular function was normal. A routine followup transthoracic echo identified a paravalvular leak in the non-coronary sinus with a *vena contracta* of 0.6 cm. Discharge plans are complete and the patient is asymptomatic. Blood cultures are negative, there is no evidence of hemolysis and the ejection fraction is 45%. Which of the following is the best treatment option?**
   A. Observation until spontaneous resolution or development of symptoms.
   B. Percutaneous catheter intervention to place an occlude device.
   C. Reoperation for valve re-replacement using a bioprosthetic valve.
   D. Reoperation for valve re-replacement using another mechanical valve.
   E. Reoperation to close the defect with pledgeted sutures.

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5. **A 78-year-old man with diabetes, high cholesterol, and well controlled hypertension presented with exertional chest pain and shortness of breath. He has never had a stroke or TIA, he lives independently and remains active. Non-specific ECG changes and criteria for left ventricular hypertrophy were present on ECG. Cardiac catheterization demonstrated severe multivessel disease with an ejection fraction of 50%, and a carotid duplex showed a 50–70% and 60–75% stenoses of the right and left internal carotid arteries, respectively. At the time of surgery the initial TEE demonstrates an aortic valve area of 1.15 cm^2 and heavy calcification of the annulus and leaflets.**

   Which of the following is the best operation for this patient?
   A. Off-pump multivessel bypass grafting alone and surveillance of the carotid stenoses and aortic stenosis
   B. Off-pump multivessel bypass grafting with anticipated percutaneous transcatheter aortic valve replacement in the near future.
   C. On-pump multivessel bypass grafting and surveillance of the carotid stenoses and aortic stenosis.
   D. On-pump multivessel bypass grafting and replacement of the aortic valve with a bioprosthetic valve.
   E. On-pump multivessel bypass grafting, bioprosthetic AVR and left carotid endarterectomy.
6. **Fifteen years ago a 75-year-old woman underwent coronary artery bypass grafting with saphenous vein grafts to the LAD, obtuse marginal, and posterior descending arteries. She developed unstable angina and a cath revealed a 90% left main stenosis and occlusions of the native right coronary and the OM and PDA grafts. There was a 90% stenosis of the saphenous vein graft to the LAD. At reoperation, a LIMA was placed to the LAD and the old saphenous vein graft was ligated. New saphenous vein grafts were placed to the obtuse marginal and PDA. The patient cannot be weaned from bypass because of left heart failure and anterior akinesis. TEE shows no valve pathology, and ultrasonic flow measurements of the LAD, OM and PDA grafts are 26, 50, and 35 mL/min respectively. Which of the following is the most appropriate action to take?**
   A. Go back on bypass and re-do the LIMA-LAD anastomosis.
   B. Place a left ventricular assist device.
   C. Remove the ligature from the saphenous vein graft to the LAD.
   D. Place an intra-aortic balloon pump and add inotropic support.
   E. Return to bypass and place a saphenous vein graft to the LAD.
7. **A 68-year-old man is about to undergo coronary bypass grafting and mitral valve surgery. Coronary angiography reveals severe 3-vessel disease and preoperative transthoracic echocardiography shows severe ischemic mitral valve regurgitation with LVEF 35% and moderate-to-severe tricuspid valve regurgitation. Pre-bypass TEE now shows mild mitral regurgitation and mild tricuspid valve regurgitation. Which of the following statements is correct?**
   A. CABG and mitral valve repair will lower PA pressure, so concomitant tricuspid annuloplasty is not indicated.
   B. A complete tricuspid ring annuloplasty is preferred to avoid future dilatation of the posterior annulus.
   C. A flexible mitral annuloplasty ring is best to preserve mitral annular mobility and ventricular contractility.
   D. The patient's poor left ventricular function suggests that concomitant tricuspid valve repair is prudent.
   E. The present TEE findings indicate that CABG alone is adequate—mitral annuloplasty is not required.
8. **A 63-year-old woman presented to the emergency department complaining of shortness of breath and recurrent chest pain. Five days before she had acute chest pain that spontaneously resolved. Her past medical history was notable only for hypertension. Physical examination confirms dyspnoea at rest. Blood pressure is 80/50, heart rate is 100, and her skin is cool and clammy. An ECG shows sinus tachycardia with ST elevations in the anterior leads. This woman's echocardiogram shows a large anterior effusion with diastolic RV collapse and impaired LV function with posterior akinesis suggesting postinfarction free wall ventricular rupture. This patient is best managed by**
   A. Angioplasty, bare metal stenting of the LAD, and delayed coronary artery bypass grafting.
   B. Beta blockers, IV fluids, and septal myomectomy when stable.
   C. Emergent circumflex CABG and myocardial reinforcement with sutures and felt pledgets.
   D. Pericardiocentesis, intra-aortic balloon placement, and inotropic support.
   E. Prompt surgical intervention with a glued epicardial patch.
9. **A 56-year-old man underwent a 3-vessel coronary artery bypass following a recent myocardial infarction. Grafts included LIMA to LAD, radial artery graft to OM1, and saphenous vein graft to the PDA. This was done on cardiopulmonary bypass with a warm beating heart. Thirty-six hours postoperatively the patient is noted to be in severe respiratory distress with increased work of breathing. He is on a face mask with 100% inspired oxygen. Pulmonary artery pressure is 55/35, cardiac index is 1.7, and mean arterial pressure is 50 mmHg. Physical exam reveals significant rales and a systolic murmur. His chest radiograph shows severe pulmonary edema. Which of the following is the next step in the management of this patient?**

A. Begin an epinephrine (adrenaline) infusion
B. Do a stat coronary catheterization
C. Initiate a furosemide infusion
D. Obtain a stat echocardiogram
E. Start a phenylephrine infusion

10. **Three months ago a 56-year-old man suffered an anterior wall myocardial infarction. An echocardiogram shows an apical aneurysm. Which of the following statements about his condition is true?**
A. All lesions of this type that exceed 3 cm should be repaired regardless of symptoms.
B. Five-year survival for asymptomatic patients with this condition is 90% with medical therapy.
C. The leading cause of death for medically managed patients with this condition is heart failure.
D. The majority of these lesions are posterior and at the base of the heart.
E. Surgical repair of the condition should be attempted before recommending transplantation.

11. **A 75-year-old man had a history of congestive heart failure, aortic regurgitation, coronary artery disease with myocardial infarction, and severe ischemic mitral regurgitation. Preoperative echo details included an ejection fraction of 30%, normal mitral leaflets, and an area of akinesis in the lateral wall. CABG, AVR and mitral repair were done. Bypass and crossclamp times were long, and he was weaned on an intra-aortic balloon pump, milrinone at 0.7 µg/(kg min) and epinephrine at 0.1 µg/(kg min). Still in the operating room now, his BP is 95/50, PA = 60/20, CVP = 17, pH = 7.25, CI = 1.5, SVO_2 = 40%, and he is making little to no urine. All grafts appear to be functioning based on Doppler interrogation and TEE shows normal prosthesis function, global LV hypokinesis, lateral wall akinesis (unchanged from preop) and no significant mitral regurgitation. The patient has been closely monitored for the last 30 min and there has been no change.**
The most appropriate next step is to
A. Add a vasoconstrictor such as noradrenaline (norepinephrine).
B. Cannulate and start venoarterial ECMO and transfer to the ITU.
C. Give bicarbonate and inhaled nitric oxide.
D. Perform additional coronary bypass grafts.
E. Place a temporary ventricular assist device.

12. **A 64-year-old man (BSA 1.9 m^2) presented with severe chest pain and cardiogenic shock. Catheterization revealed severe triple vessel disease. An intra-aortic balloon pump did not stabilize his hemodynamics so emergent on-pump CABG x 4 was done (LIMA to LAD, SVG to PDA, and sequential SVG to OM1 and OM2). He was weaned from cardiopulmonary bypass with four drugs and the balloon pump, but hemodynamics deteriorated following chest closure and bypass was reinstated. TEE revealed poor left ventricular function with anteroapical wall akinesis. A saphenous vein graft was placed to the LAD distal to the LIMA anastomosis to no avail. A short-term LVAD was placed with left atrial inflow via the right superior pulmonary vein and an outflow graft anastomosed to the ascending aorta. The next day his hemodynamics included: LVAD flow 4.0 L/min, PA 33/25 (mean 29), RA 27, heart rate 95. His urine output was 20 mL/h on a furosemide drip at 20 mg/h. Serum creatinine was 2.5 mg/dL (rising), and he remained coagulopathic despite massive blood component transfusion. Reoperation is now considered necessary and the short-term device is to be replaced with a long-term LVAD as a bridge to transplant. The most life-threatening complication anticipated for this patient is**
A. Bleeding from the left ventricular apical LVAD cuff suture line.
B. Bleeding from the outflow graft anastomosis on the ascending aorta.
C. Hepatic failure.
D. Renal failure.
E. Right ventricular failure.

13. **Regarding using an LVAD as bridge to transplantation, which of the following statements is correct?**
A. Early RVAD placement is necessary in approximately 10% of LVAD-bridged patients.
B. Excessive postoperative bleeding occurs in less than 20% of patients.
C. The incidence of postoperative stroke and other thrombotic complications is about 5%.
D. Infection is encountered equally with pulsatile and continuous flow devices.
E. One-year post transplant survival is worse for bridged compared to non-bridged patients.

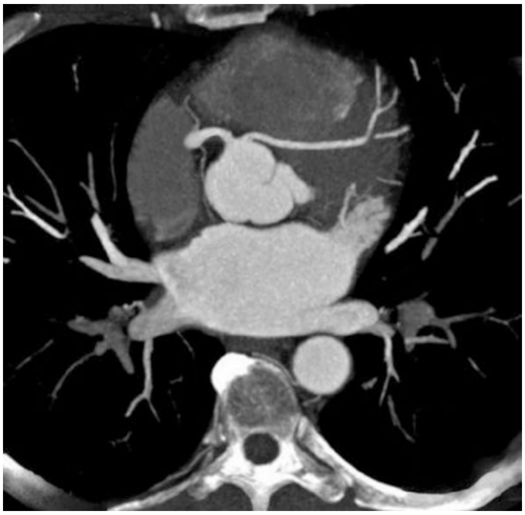
14. **A 26-year-old man was readmitted with heart failure and fluid overload. Consequences of his dilated cardiomyopathy prompted several admissions over the last 6 months despite optimal medical management and compliance with medications. Recently he had two episodes of non-sustained ventricular tachyarrhythmia. He weighs 250 lb and has blood type O. There is no significant comorbidity. The most recent cath data is: BP 88/70, CVP 6, PA 56/26 (mean 36), PCWP 19, CO 3.8, CI 1.6, transpulmonary gradient (TPG) 17, pulmonary vascular resistance (PVR) 5.0 Woods units. He was then challenged with nitroprusside 80 µg/kg/min and milrinone 0.37 µg, and hemodynamics were: BP 86/58, CVP 8, PA 67/28 (mean 43), PCWP 20, CO 4.1, CI 1.71, TPG 18, and PVR 5.6. The appropriate management recommendation is**
A. Begin chronic IV milrinone and reassess PVR after 3 months.
B. Continuous outpatient management and list for transplantation (status 2).
C. Emergency cardiac transplantation.

D. Prepare for elective LVAD placement with apical cannulation.
E. Start IV milrinone, place an ICD and list for transplantation (status 1B).

15. **A 68-year-old man had aortic valve replacement with a bileaflet mechanical valve and CABG to the posterior descending artery 12 years ago. He now has severe heart failure but is not a transplant candidate due to chronic lymphocytic leukemia that has been in remission. Which of the following statements is true?**
A. Another cardiac catheter is not necessary as the left ventricle will be defunctionalized.
B. Destination LVAD is possible, but the mechanical valve must be changed to a bioprosthesis.
C. Echo demonstration of severe right ventricular failure mandates BiVAD destination therapy.
D. This patient is not a candidate for destination therapy due to the mechanical prosthesis.
E. The patient's aortic valve should be sewn shut or patched closed if an LVAD is placed.

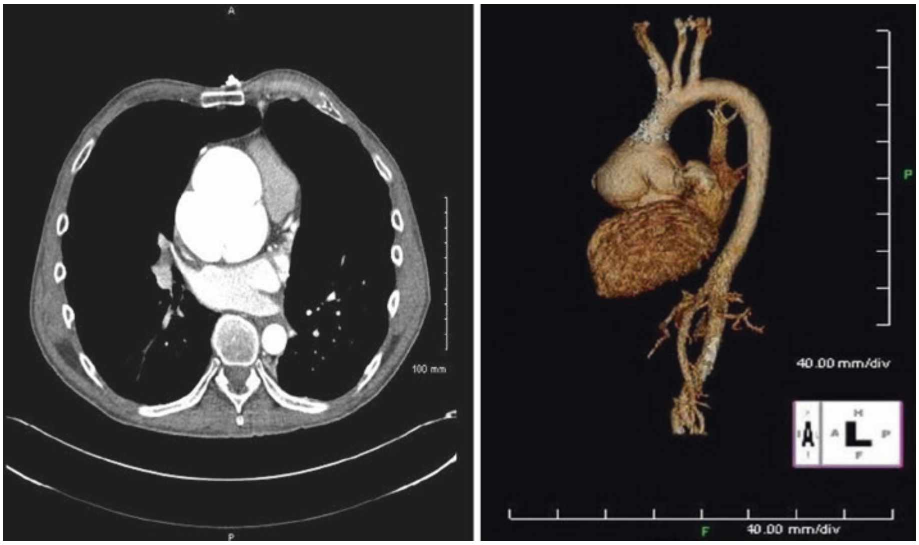
16. **A 71-year-old man is undergoing a 4-vessel CABG and mitral valve repair the day after failed percutaneous angioplasty of the right coronary artery for an acute myocardial infarction. He cannot be separated from bypass despite two high-dose inotropes and an intra-aortic balloon pump. Of the following choices the best strategy to deal with this includes**
A. BiVAD support with short-term external ventricles, cannulating the LV apex for LVAD inflow.
B. BiVAD support with short-term external ventricles, cannulating the LA for LVAD inflow.
C. Percutaneous LA and femoral cannulation for left ventricular support with an external device.
D. Placing a long-term internal mechanical ventricle as destination therapy.
E. Withdrawal of support because of patient age and overwhelming mortality of this condition.

17. **A 59-year-old man experienced increasing angina during routine activities. He had two episodes during hemodialysis last week and was admitted for further workup. A high resolution CT slice is shown.**



The findings are significant for
A. accelerated coronary atherosclerosis.
B. associated valvular anomalies.
C. exercise-induced coronary spasm.
D. increased risk of sudden death.
E. right ventricular failure.

18. **A 44-year-old man presented with increasing dyspnoea. Echocardiography revealed severe aortic valve regurgitation associated with an aortic aneurysm. Parts of a CT study are shown. The patient has no signs of a heritable connective tissue disorder. During surgery the aortic valve is trileaflet, the left coronary leaflet is prolapsed, and each of the cusps has fenestrations near the commissures.**



The best operation for this patient is

A. aortic valve replacement with a mechanical prosthesis and separate replacement of the tubular portion of the ascending aorta with a prosthetic graft.
B. replacement of the aortic root with a composite valve graft and reattachment of coronary arteries with a 10-mm prosthetic graft (Cabrol procedure).
C. replacement of the aortic root with a cryopreserved homograft and direct reattachment of the coronary buttons to the homograft.
D. replacement with a composite mechanical valve graft and direct reattachment of the coronary buttons to the graft (modified Bentall procedure).
E. valve-sparing aortic root replacement with direct reattachment of coronary artery buttons to the prosthetic graft (David reimplantation procedure).

19. **An asymptomatic 22-year-old man with Marfan syndrome was referred for evaluation of an ascending aortic aneurysm measuring 5.0 cm in diameter. He has been compliant with his β-blocker regimen but he is concerned because his sister had an aortic dissection at age 26. An echocardiogram shows normal aortic valve function and normal ventricular function.**

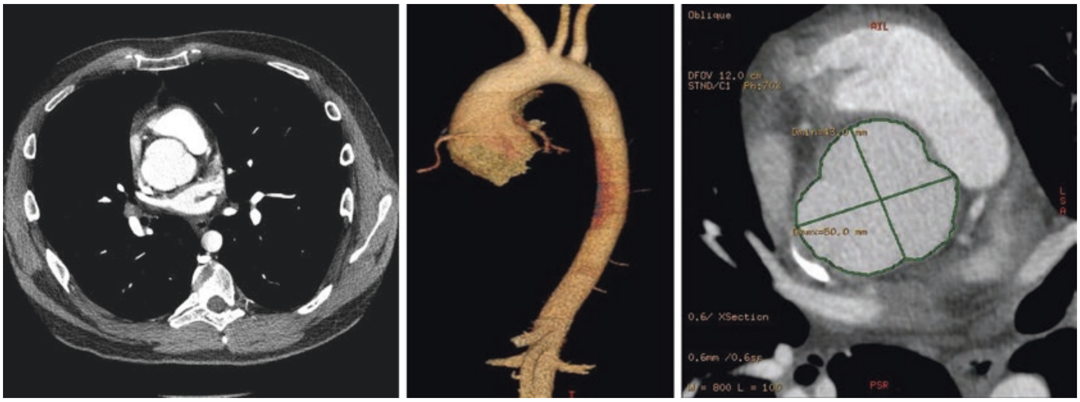
    The most appropriate management is to

    A. continue treatment with beta blockers and repeat the echocardiogram if symptoms develop.
    B. continue treatment with beta blockers and repeat echocardiogram in 6–12 months.
    C. schedule elective graft replacement of the ascending aorta.
    D. schedule elective valve-sparing root replacement.
    E. stop the beta blockers, begin oral losartan, and repeat the echocardiogram in 6–12 months.

20. **The mutation causing Marfan syndrome most frequently involves the gene for**

    A. Elastin
    B. Fibrillin-1
    C. Transforming growth-β
    D. Type I collagen
    E. Type III collagen

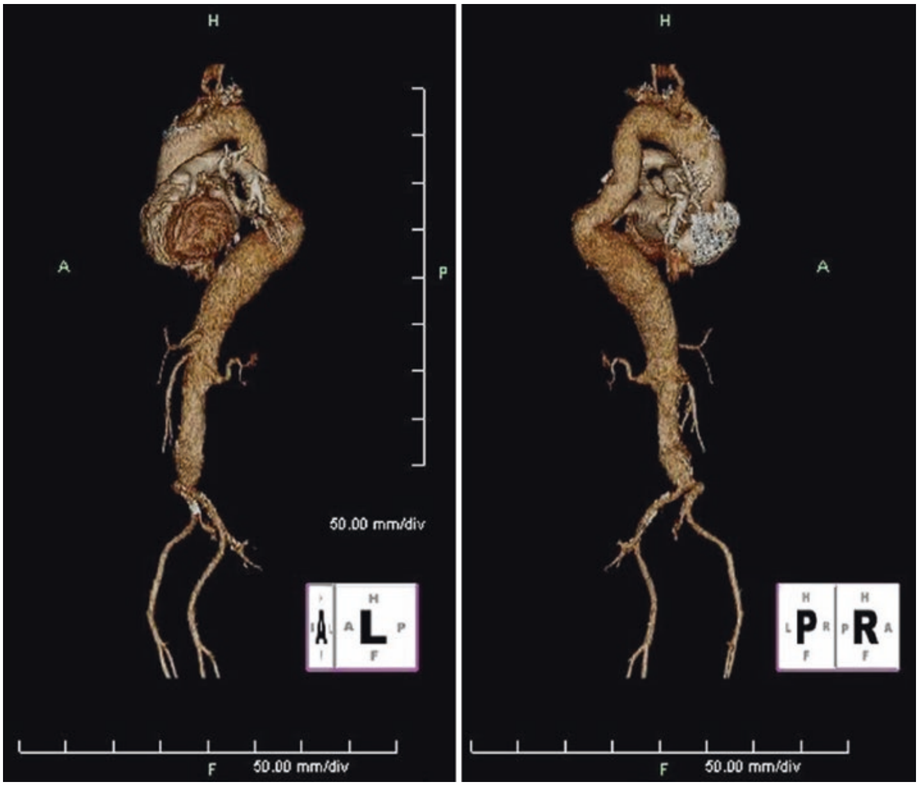
21. **A 30-year-old man with no symptoms requested evaluation of his thoracic aorta. His father died suddenly at age 41 from an aortic dissection. On physical examination his height and wing span are 195 cm and 203 cm, respectively. The arch of his palate is remarkably high and striae are noted on his abdominal flanks. His fingers are long and spindly, and his knee joints are hyperextensible bilaterally. He suffered a dislocated lens in his right eye at age 19. Parts of a CT angiogram study are shown with maximum aortic root dimension of 50.0 mm.**



Which of the following is the most important management strategy for this patient?

A. Aortic root replacement with a mechanical valved conduit.
B. Losartan therapy and a follow-up CT angiogram in 12 months.
C. A modified remodeling (Yacoub) procedure with replacement of the non-coronary sinus.
D. Valve-sparing aortic root and total aortic arch replacement.
E. A Wheat procedure.

22. **A 60-year-old woman presented with a 4 month history of increasing back pain. An echocardiogram revealed normal valve function and a left ventricular ejection fraction of 0.45. Two CT angiogram images are shown. There was no evidence of coronary artery disease on her electrocardiogram or myocardial perfusion scan.**



The most appropriate plan of treatment is

A. Graft replacement of the ascending aorta and transverse aortic arch during an initial operation, followed by graft replacement of the thoracoabdominal aorta as a subsequent operation.

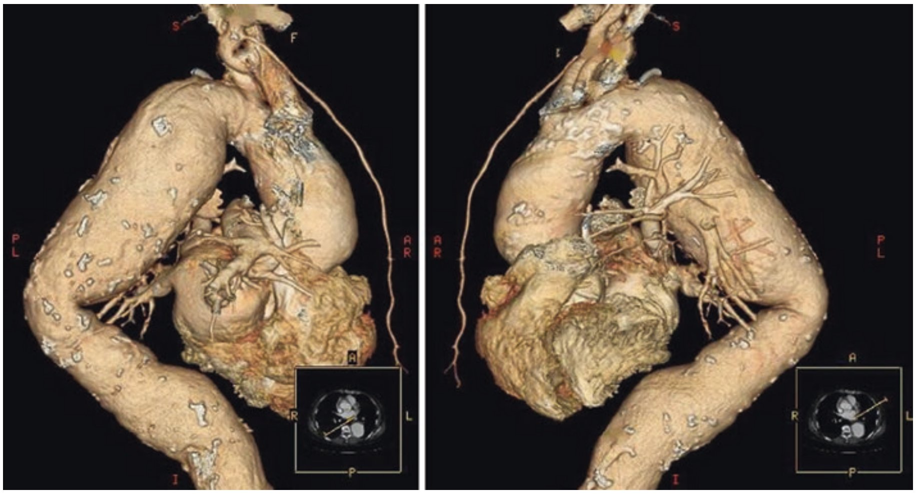
B. Graft replacement of the ascending aorta during an initial operation, followed by graft replacement of the thoracoabdominal aorta as a subsequent operation.

C. Graft replacement of the ascending aorta, transverse aortic arch, and thoracoabdominal aorta during a single operation.

D. Graft replacement of the thoracoabdominal aorta during an initial operation, followed by graft replacement of the ascending aorta and transverse aortic arch as a subsequent operation.

E. Graft replacement of the thoracoabdominal aorta during an initial operation, followed by graft replacement of the ascending aorta as a subsequent operation.

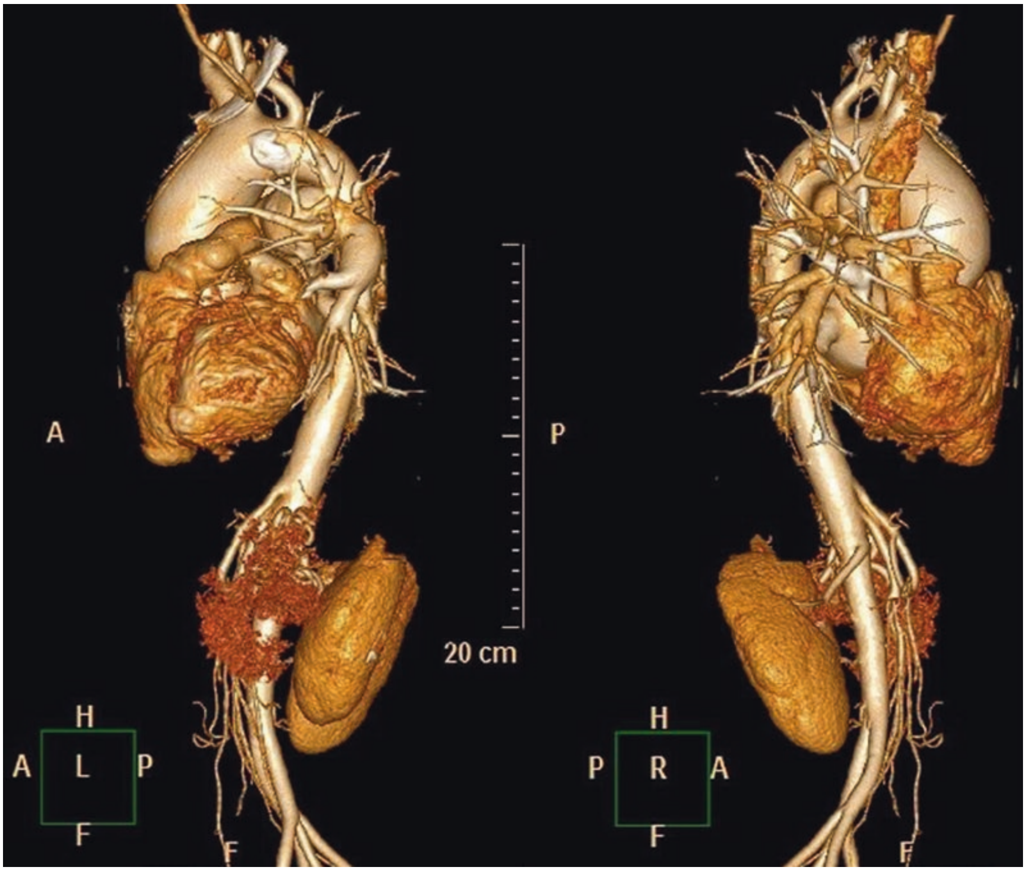
23. **A 68-year-old woman has no pain, but she does complain of dyspnea when climbing more than one flight of stairs. She has lower extremity edema on examination. An echocardiogram reveals a bicuspid aortic valve with severe regurgitation, a dilated ascending aorta, and a left ventricular ejection fraction of 35%. The diameter at the sinotubular junction is 2.8 cm. Cardiac catheterization confirms these findings and reveals no significant coronary artery stenoses. A CT angiogram of the aorta is shown.**



The best plan to stage surgical treatment in this patient is

A. AVR and graft replacement of the ascending aorta and transverse aortic arch with elephant trunk during the first operation, then subsequent thoracoabdominal repair.
B. graft replacement of the thoracoabdominal first, then valve-sparing aortic root replacement and graft replacement of the ascending aorta and transverse aortic arch later.
C. initial AVR, followed by graft replacement of the thoracoabdominal aorta during a second operation.
D. thoracoabdominal aortic graft replacement first, followed by AVR and graft replacement of the ascending aorta and transverse arch during the second operation.
E. valve-sparing aortic root replacement and graft replacement of the ascending aorta and transverse aortic arch initially, then graft replacement of the thoracoabdominal aorta later.

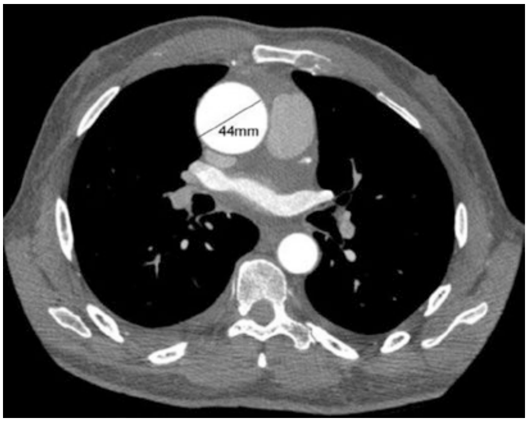
24. **A 58-year-old woman reported increasing retrosternal pain and dyspnoea over the past 3 months. Images from her CT reconstruction are shown. Other studies revealed moderate-to-severe aortic valve regurgitation but minimal calcification of the aortic valve and aorta. AVR and graft replacement of the ascending aorta and lesser curvature of the aortic arch (beveled hemi-arch repair) is now underway. Cannulation was via the right axillary artery for arterial inflow, a single right atriocaval cannula for venous drainage, a left ventricular vent through the right superior pulmonary vein, and a retrograde cardioplegia cannula. Systemic cooling was initiated immediately and ventricular fibrillation occurred at a venous return temperature of 31 °C. Soon afterward the left ventricle became markedly distended and the perfusionist reported copious return from the left ventricular vent.**



The most appropriate way to manage this situation is to

A. Deliver continuous retrograde cardioplegia until the patient has been cooled enough that circulatory arrest can be initiated.
B. Fill the pericardium with iced saline and continue rapid cooling until the patient has been cooled enough that circulatory arrest can be initiated.
C. Place a clamp across the aneurysmal ascending aorta and deliver antegrade cardioplegia through a needle placed in the ascending aorta.
D. Place a clamp across the aneurysmal ascending aorta, open the aneurysm, and deliver antegrade cardioplegia through coronary ostial cannulas.
E. Place an additional ventricular vent directly through the left ventricular apex.

25. **A 62-year-old with a benign past medical history developed an upper respiratory illness. Chest radiograph revealed a prominent upper mediastinum, prompting a subsequent chest CT (see figure). On current examination he is 73 in. tall, weighs 195 lb, vital signs are normal, and his physical exam is unremarkable.**



Which of the following is the most appropriate next step in his management?

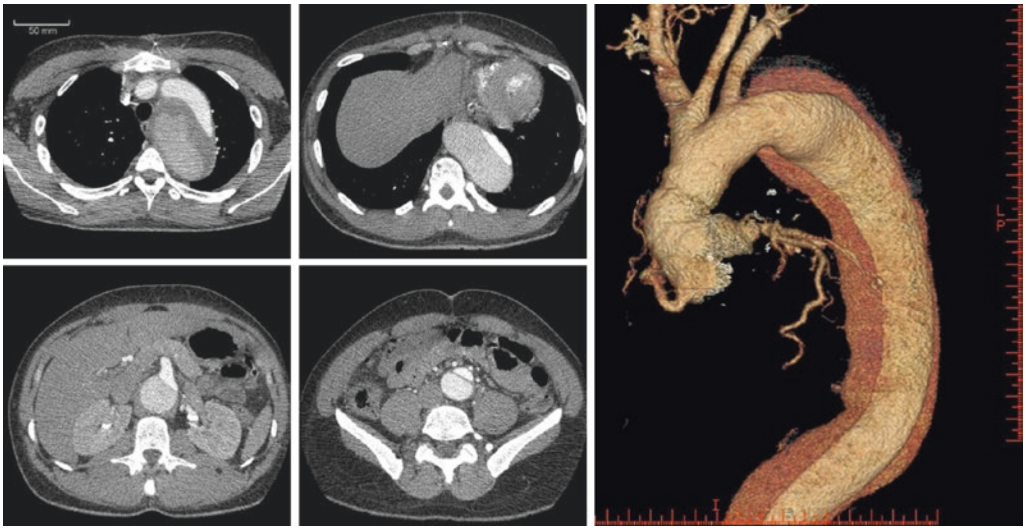
A. Aortic root and ascending aortic replacement with hemiarch reconstruction.
B. Aortic root replacement.
C. Ascending aortic replacement.
D. CT angiogram in 12 months.
E. Oral losartan.

26. **A 67-year-old woman was referred for treatment of symptomatic aortic valve disease. Transthoracic echo showed severe calcification of the aortic valve with fusion of right and noncoronary cusps, severe stenosis, and moderate regurgitation. At operation, TEE also revealed substantial atheroma within the ascending and descending thoracic aorta. Epi-aortic ultrasound showed atherosclerotic thickening exceeding 5 mm throughout the distal two-thirds of the ascending aorta and the proximal portion of the aortic arch.**

The best strategy for arterial cannulation and cardiopulmonary bypass (CPB) for this patient is

A. Arch cannulation, CPB with moderate hypothermia, and cardioplegic arrest while the distal ascending aorta is clamped.
B. Femoral cannulation, CPB and deep hypothermic circulatory arrest without aortic clamping.
C. Femoral cannulation, CPB with moderate hypothermia, and cardioplegic arrest while the distal ascending aorta is clamped.
D. Right axillary cannulation, CPB and deep hypothermic circulatory arrest without aortic clamping.
E. Right axillary cannulation, CPB with moderate hypothermia, and cardioplegic arrest while the distal ascending aorta is clamped.

27. **A 38-year-old hypertensive man had a type A aortic dissection 5 years ago and underwent proximal aortic repair with ascending aortic and hemiarch replacement. A residual type B aortic dissection was subsequently followed. He was lost to follow-up for 18 months, but returned with upper back pain between his spine and left scapula. Despite his antihypertensive regimen of metoprolol, clonidine, amlodipine, doxazosin, and minoxidil, he presents with a blood pressure of 180/110 mmHg. He is otherwise healthy and active. Four CT angiogram frames and a reconstruction image are shown.**

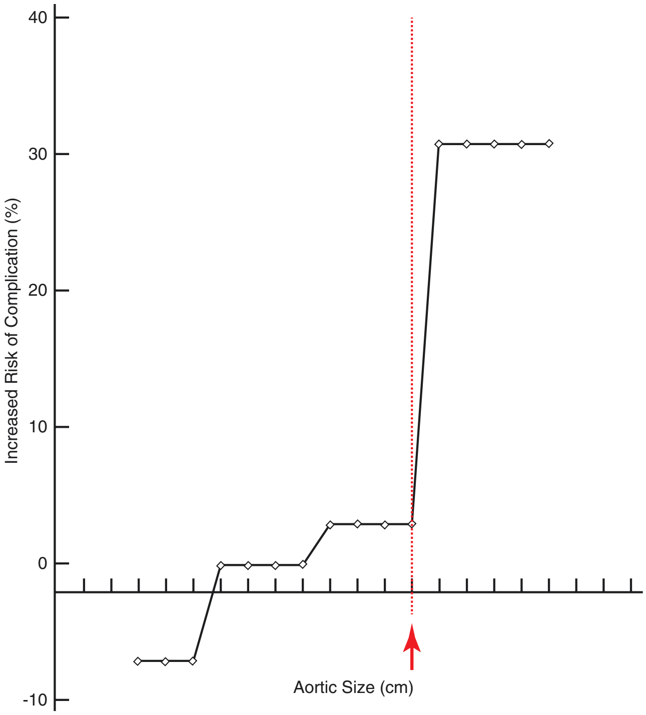


Which of the following is the appropriate next step in his management?

A. Continued surveillance imaging and adding labetalol 300 mg TID to his medical regimen
B. Descending thoracic aortic replacement using a clamp and sew technique
C. Extent I thoracoabdominal aortic replacement using left heart bypass

D. Extent II thoracoabdominal aortic replacement using a temporary axillofemoral shunt
E. Thoracic endovascular aortic repair using a stent-graft

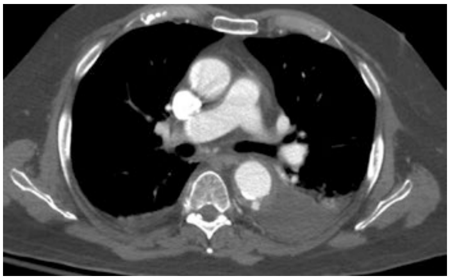
28. **Regression analysis of robust natural history data from patients with ascending aortic aneurysms has been used to determine the diameter at which the probability of rupture or acute dissection increases significantly. At this "hinge point" (arrow in the figure), patients become 30% more likely to have a complication such as ascending aortic dissection or rupture during their lifetime.**



The diameter at which this hinge point occurs is

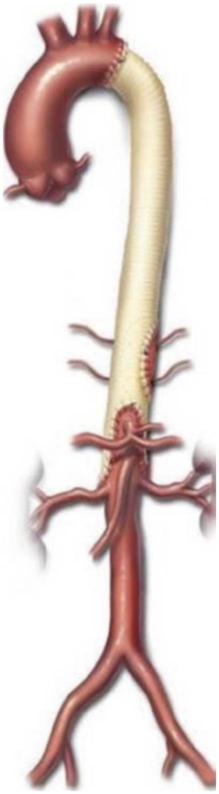
A. 4
B. 5
C. 6
D. 7
E. 8

29. **A 75-year-old man presented to the ER complaining of tearing pain in his back. His blood pressure was 190/110, HR was 90 and rhythm was normal sinus. A representative frame from his CT angiogram is shown. Which of the following is the most appropriate management?**



A. Bedrest with strict BP control using esmolol and nitroprusside
B. Endoaortic stent graft placement for the type B dissection
C. Immediate operative repair of the ruptured type B dissection
D. Immediate surgical repair of his type A dissection
E. Replacement of the descending aorta for the type B dissection

30. **A 68-year-old woman underwent a Crawford extent I graft repair of a thoracoabdominal aortic aneurysm (see figure). Adjuncts used during the repair included left heart bypass, selective visceral perfusion, and cerebrospinal fluid drainage. The patient was extubated on the first postoperative day and the cerebrospinal fluid drainage catheter was taken out 1 day later. Six hours after the catheter was removed the patient complained of severe headache. She is in sinus rhythm with a heart rate of 92 and a blood pressure of 148/82 mmHg. The previous spinal catheter site is dry and without evidence of bleeding or inflammation. White blood cell count = 6.8K/mm^3, hemoglobin = 10.3 g/dL, platelet count = 122,000/mm^3, glucose = 98 mg/dL, and creatinine = 1.1 mg/dL.**



The most appropriate initial management is to

A. continue observing the patient and keep her on strict bed rest
B. do a lumbar puncture for CSF studies and start IV antibiotics

C. obtain an immediate brain CT scan
D. place an epidural blood patch
E. reinsert the spinal drain and reduce intrathecal pressure to 10–15 mmHg

31. **A 45-year-old man underwent repair of a thoracoabdominal aortic aneurysm 72 h ago. He emerged from anesthesia with a normal neurologic exam but required continued ventilator support due to respiratory insufficiency and copious bronchial secretions. He was started on a propofol infusion for sedation and the nurse soon noted that he is no longer able to move his lower extremities. His blood pressure is 90/40 mmHg, CVP is 16, and his intrathecal pressure is 15 mmHg.**

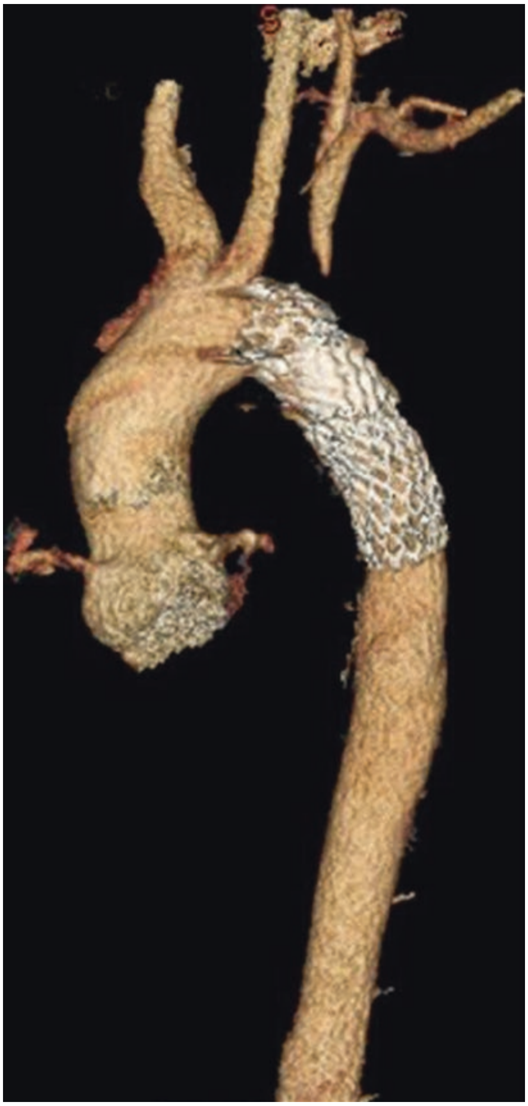
    Which of the following is the most important initial step in caring for this patient?

    A. Administer a bolus of naloxone and discontinue the propofol
    B. Consult neurosurgery to place a lumbar cerebrospinal fluid (CSF) drain
    C. Discontinue the propofol infusion and start a nicardipine infusion
    D. Get an MR angiogram of the thoracic aorta to evaluate his spinal arterial supply
    E. Stop the propofol infusion and administer a norepinephrine infusion

32. **A 63-year-old man with an aneurysmal chronic aortic dissection underwent Crawford extent II graft replacement of the entire thoracoabdominal aorta (see figure). The aortic reconstruction included reimplanting the 11th and 12th intercostal arteries. He awoke neurologically intact, was extubated on the first postoperative day, and was transferred out of the ICU on POD# 3. However, the next morning he reported being unable to stand. On exam he is afebrile, his pulse is regular at 86, and BP is 148/78. He is alert, is breathing comfortably, and his mental status, sensation, and upper extremity strength are normal. While supine, he is able to lift both legs against gravity but not against resistance. Labs include: WBC 8.6K/mm^3, hemoglobin 9.8 g/dL, hematocrit 30.8%, platelet count 138K/mm^3, glucose 105 mg/dL, and creatinine 0.9 mg/dL. The most appropriate immediate action is to**

    A. Administer intravenous heparin
    B. Begin IV phenylephrine infusion to raise MAP over 90 mmHg
    C. Insert a lumbar drain and remove cerebrospinal fluid
    D. Obtain a thoracic aortogram to assess the patency of intercostals arteries
    E. Transfuse one unit of packed red cells

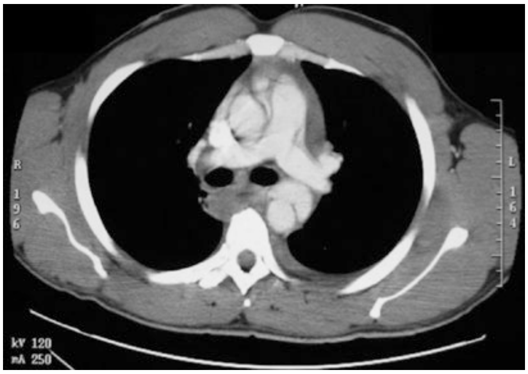
33. **A 34-year-old woman sustained multiple injuries from a motor vehicle accident 18 months ago including a pelvic fracture, pulmonary contusions, and aortic transection at the isthmus. Her aortic injury was treated by thoracic aortic endovascular repair with a stent graft and her pelvis was repaired by internal fixation. She recovered from her injuries, however for the last several months she complained of becoming acutely lightheaded while exercising. On two occasions in the last month she had syncopal episodes while using an elliptical trainer. On physical examination her right and left arm blood pressures are 140/80 mmHg and 120/70 mmHg, respectively. A surveillance CT angiogram is shown.**



    Which of the following is the most appropriate next step in the management?

    A. Carotid ultrasound and Doppler assessment
    B. Cerebral angiogram to determine blood flow patterns
    C. Coil embolization of the left subclavian artery
    D. Left carotid to subclavian bypass
    E. Left vertebral artery bypass

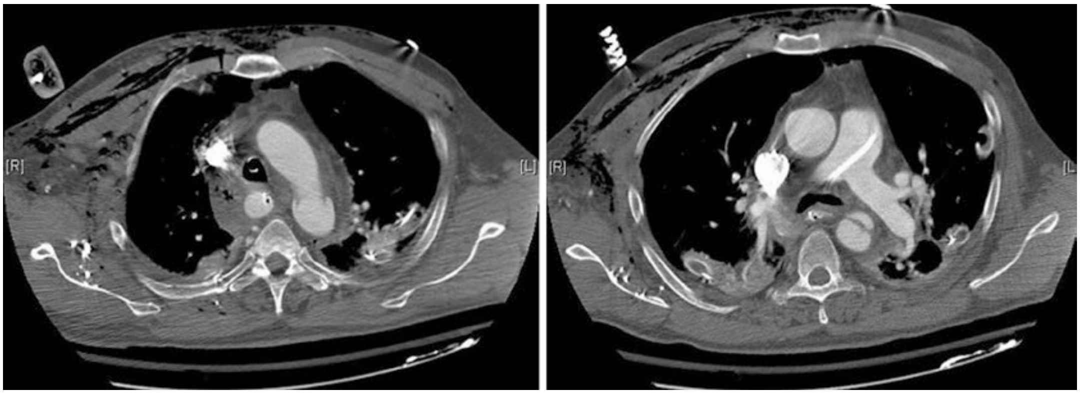
34. **A 26-year-old man is brought into the emergency department following a high-speed motor vehicle accident. He is awake and alert but complaining of abdominal pain. The chest radiograph reveals no pneumothorax, but he does have three rib fractures on the left. A CT scan of the chest, abdomen, and pelvis reveals a contained partial aortic transection in the chest (see figure) and free blood in the abdomen with a suggestion of a splenic laceration.**



The most appropriate management of this patient's injuries is

A. Exploratory laparotomy followed by open surgical repair of the aortic injury.
B. Open surgical repair of the aortic injury with an interposition graft by clamp-and-sew technique followed by exploratory laparotomy.
C. Open surgical repair of the aortic injury with an interposition graft utilizing femoral vein-to-femoral artery cardiopulmonary bypass, followed by exploratory laparotomy.
D. Stent graft repair of the aortic transection followed by exploratory laparotomy to repair the intra-abdominal injuries.
E. Exploratory laparotomy to repair the abdominal injuries and observation of the aortic injury with serial CT scans.

35. **A 29-year-old man was ejected during a high-speed motor vehicle collision. He was intubated in the field and remained hemodynamically stable, but he was still unarousable to verbal stimuli upon ER arrival. He has a right femur fracture and he withdraws to painful stimuli with all four extremities. Brain CT shows frontal lobe contusions, minimal edema and no frank intracranial hemorrhage. Abdominal CT shows no free air or solid organ injury. Chest CT frames are shown.**



The best management for this patient is

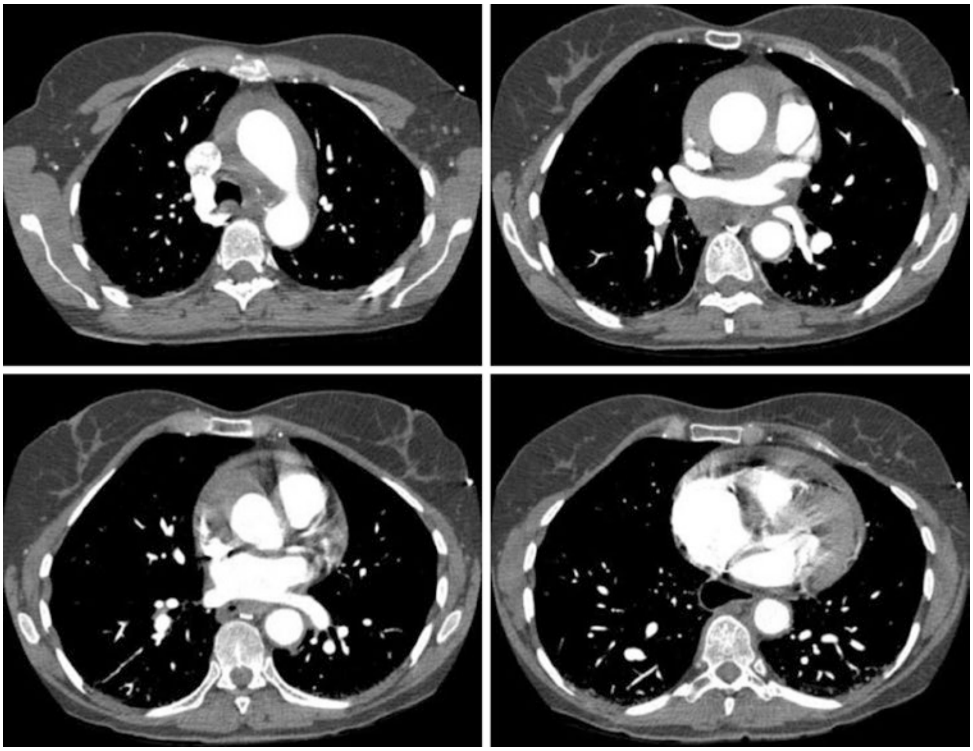
A. craniectomy, then descending aortic replacement using left heart bypass
B. endovascular stent grafting of the proximal descending thoracic aorta
C. intracranial ventriculostomy in the ICU and IV nitroprusside for BP control
D. thoracotomy and aortic wrapping with a Dacron patch or prosthesis
E. thoracotomy for descending aortic replacement under hypothermic circulatory arrest

36. **A 52-year-old man presented with an acute aortic dissection originating in the aortic root that extended beyond the aortic bifurcation. He was taken to the operating room and right radial and left femoral arterial lines were placed for blood pressure monitoring. After sternotomy he was placed on cardiopulmonary bypass via right femoral arterial and right atrial cannulation. During systemic cooling the right radial arterial pressure acutely fell to a mean pressure of 35 mmHg while the left femoral arterial pressure was 70 mmHg. The perfusionist noted an increase in the resistance of the bypass circuit. Which of the following is the correct response to this situation?**

A. Accelerate the cooling process and proceed with aortic repair
B. Apply an aortic cross-clamp and administer cardioplegia
C. Cannulate the right subclavian artery for antegrade perfusion

D. Recannulate and perfuse through left femoral artery
E. Rewarm the patient

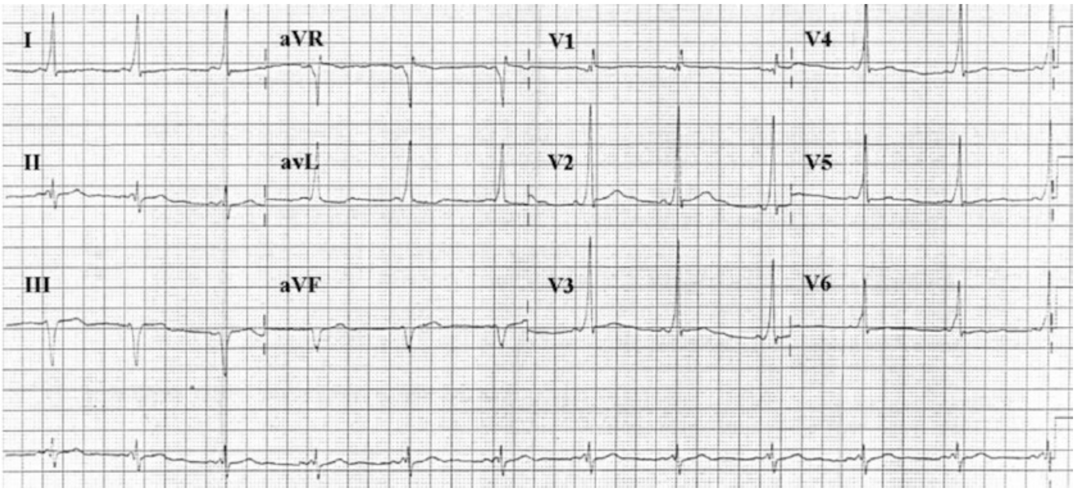
37. **A previously healthy 75-year-old woman experienced acute, severe upper chest pain radiating to her neck. On initial examination she is neurologically intact complaining only of this chest pain. Her blood pressure is 88/40 mmHg. ECG confirms normal sinus rhythm with a rate of 88 and no significant ST changes. Chest radiograph is also unremarkable. CT angiography frames are shown.**



Which of the following is the most appropriate strategy to manage this patient?

A. Admission to the intensive care unit, intravenous labetalol, and echocardiogram
B. Aortic root and ascending aortic replacement with a mechanical valved conduit
C. Aortic valve resuspension, ascending aortic and hemiarch replacement
D. Endovascular placement of a thoracic aortic stent graft
E. Total arch replacement with an elephant trunk

38. **A 45-year-old, healthy, active man had a near-syncopal episode when exercising. Further history revealed repetitive palpitations over the past few years, which his family physician was treating with a beta blocker. The patient is currently asymptomatic. A current ECG is shown.**



The most effective management for this patient is

A. Atrioventricular nodal ablation and dual-chamber pacemaker insertion
B. Dofetilide 500 µg twice daily
C. Percutaneous ablation of the bundle of Kent
D. Percutaneous left atrial ablation
E. A thoracoscopic Maze procedure

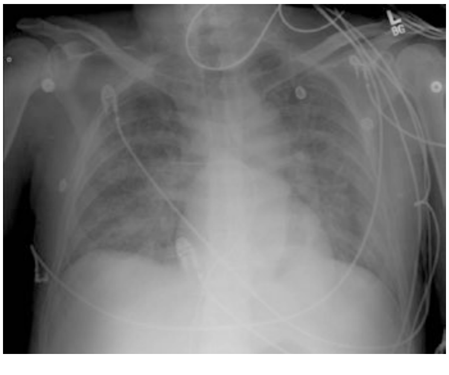
39. **A 56-year-old man underwent an orthotopic heart transplant for idiopathic dilated cardiomyopathy. Baseline creatinine was 1.4. Drug support on arrival in ICU included epinephrine 2 µg/(kg min) and isuproterenol 0.02 µg/(kg min). He was given tacrolimus 2 mg sublingually, methylprednisolone 125 mg IV q 8h to be followed by a prednisone taper, and mycophenolate mofetil 1 g IV q 12h. He was extubated 6 h postop. Hemodynamics remained stable but urine output progressively dropped to 20–30 cc/h 36 h postop and creatinine is now 3.2. Which of the following medication changes should be made?**

A. Hold all immunosuppression
B. Hold the methylprednisolone
C. Hold the mycophenolate mofetil dose once and resume at half dosage
D. Hold the tacrolimus dose
E. No changes are needed

40. **Maintenance immunosuppression following cardiac transplantation typically consists of "triple therapy". Which of the following combination is an established regimen?**

A. Cyclophosphamide, steroids and azathioprine
B. Cyclosporine, OKT3 and steroids
C. Cyclosporine, prednisolone, azathioprine
D. Tacrolimus, cyclosporine and rapamycin
E. Tacrolimus, mycophenolate mofetil and azathioprine

41. **A 55-year-old man was been treated for fever of unknown origin on the medical service for 2 weeks. His admitting symptoms consisted of progressive malaise, fever, chills, and arthralgias. Lab results included pancytopenia, hyperuricemia, and 2/2 blood cultures were positive for *Enterococcus faecalis*. Worsening renal failure required hemodialysis (present creatinine 6.4, BUN 68). His chest radiograph is shown. Cardiac echo showed 4+ aortic regurgitation and leaflet vegetations.**



Which of the following is the best management for this patient?

A. ECMO, diuresis, antibiotics, AVR after there is evidence of complete eradication of sepsis
B. Immediate aortic valve replacement and culture-directed postoperative IV antibiotics for 6 weeks
C. IV antibiotics, CT scan of abdomen and brain, emergent AVR if no contraindications are found on head CT scan
D. No cardiac operation due to end-stage presentation and severe comorbidities (renal failure and CHF)
E. PICC line, 6 weeks course of intravenous antibiotic therapy followed by aortic valve replacement

42. **A 72-year-old man is in the coronary care unit in pulmonary edema. He was generally healthy until the preceding 2 weeks of shortness of breath on exertion, malaise, low grade fevers, and night sweats. On examination he has a loud apical systolic murmur and scattered bilateral rales. A recent echocardiogram revealed an anterior leaflet perforation and a mobile vegetation that measured 1 cm in diameter. Lab results include an erythrocyte sedimentation rate of 81 mm/h and a WBC of 32,000. Multiple blood cultures drawn 24 h ago in his primary care physician's office are now positive for *Streptococcus bovis*. He is currently receiving appropriate antibiotics and aggressive diuretic therapy.**

Which of the following most strongly indicates that surgery should be performed urgently in this patient?

A. the anterior leaflet perforation
B. the 1 cm mobile vegetation
C. the pulmonary oedema
D. WBC = 32,000
E. *Streptococcus bovis* endocarditis

43. **A 99-year-old man who was reportedly normally functioning presented with acute shortness of breath followed by syncope. After stabilization, his blood pressure without pharmacologic support is 110/80 and he is obtunded but responds to pain. His echocardiogram demonstrates akinesis of the anterior wall, posterior wall and apex (LVEF = 27%) with aortic stenosis (calculated valve area = 0.4 cm^2), three plus mitral regurgitation, and an estimated pulmonary artery pressure of 80 mmHg. A CT angiogram suggests significant proximal LAD and RCA stenoses. BNP on admission was 2000 ng/L. Troponin levels are pending. The family wants everything done. Of the following choices the appropriate recommendation to the family and primary physician is**

A. Candid end-of-life discussion and hospice care
B. Cardiac cath with angioplasty and stenting of the LAD and RCA
C. A milrinone bolus followed by infusion and re-evaluation

D. Minimally invasive aortic valve replacement and double coronary artery bypass
E. Placement of an intra-aortic balloon pump and re-evaluation

44. **A 45-year-old woman complained of dyspnea on exertion (noted after two flights of stairs). Her history included rheumatic fever during childhood. Her transthoracic exercise echocardiogram documented mitral valve stenosis (valve area = 1.5 cm^2) with immobile and calcified leaflets (Wilkins Score = 10), preserved left ventricular function, an estimated systolic pulmonary artery pressure of 54 mmHg, and a mean valve gradient of 10 mmHg.**

The most appropriate management is

A. Mitral valve replacement with a mechanical valve
B. Mitral valve replacement with a tissue valve
C. Open surgical commisurotomy
D. Percutaneous mitral balloon valvotomy
E. Repeat clinical assessment in 6–12 months

45. **A 73-year-old woman became acutely short of breath and coughed up thin sputum. In the emergency department her heart rate was 120/min and blood pressure was 90/40. She was immediately intubated and cardiac catheterization showed severe 3-vessel coronary disease with an occluded distal right coronary artery that faintly reconstitutes via collaterals from the anterior descending. An echo showed 4+ mitral regurgitation with flail chords. A family member indicated that the patient had severe chest pain 5 days ago with intermittent mild-to-moderate chest pain since. Emergent CABG and mitral repair was done, which included reattaching the papillary muscle and placing an annuloplasty ring. After weaning from cardiopulmonary bypass the transesophageal echo showed 3+ mitral regurgitation.**

Which of the following statements about this case is most accurate?

A. Cardiopulmonary bypass should be resumed and chordal sparing mitral valve replacement performed
B. Concurrent revascularization was unnecessary since the main cause of her acute deterioration was the regurgitation
C. The observed mitral regurgitation will improve, therefore, no further intervention is necessary
D. Since the major cause of cardiogenic shock is mitral regurgitation perioperative mortality is low when mitral competence is re-established
E. Temporary mechanical support with an LVAD is indicated to allow the infarction to heal and mitral regurgitation to resolve

46. **A 35-year-old asymptomatic woman had severe mitral regurgitation due to long standing Barlow's disease. Mitral valve repair was recommended due to new onset atrial fibrillation. Intraoperative valve analysis confirmed a large valve with excess tissue and bileaflet prolapse. Operation included triangular P2 resection, posterior commissuroplasty, PTFE neo-chordae to the A2, P2 and P3 segments, and a size 40 mm semi-rigid complete annuloplasty ring. She was separated from cardiopulmonary bypass easily on a low dose of epinephrine and with normal pulmonary pressures and a CVP of 14. The post-repair TOE shows systolic anterior motion. The epinephrine was stopped and CVP was increased to 16 mmHg with volume loading, but the findings persisted. Cardiopulmonary bypass was reinstituted.**

Which of the following is the best course of action?

A. Anterior leaflet resection
B. Mitral valve replacement
C. Placement of a larger annuloplasty ring
D. Replacement of the ring with an incomplete flexible band
E. Sliding posterior leaflet plasty

47. **An otherwise healthy 50-year-old, asymptomatic man has severe mitral valve regurgitation due to Barlow's disease and preserved left ventricular function. Which of the following is the most relevant to determine whether to proceed with mitral valve surgery at this time?**

A. Accessibility to a center performing a high volume of mitral valve operations
B. Age of the patient
C. High probability of valve repair based on the echo findings
D. Potential candidacy for warfarin therapy
E. A pulmonary artery pressure of 44/28 mmHg

48. **Which of the following conditions is a contraindication to mitral valve surgery via a right mini-thoracotomy approach?**

A. A need for concomitant tricuspid valve operation
B. Obstructive peripheral vascular disease
C. Pectus carinatum
D. Previous CABG surgery
E. Previous right pleurodesis

49. **A 75-year-old woman had severe hypertension and moderate mitral regurgitation with minimal annular calcification. You have just completed an uncomplicated coronary artery bypass × 3 and mitral valve repair. As you are removing the retrograde cannula and preparing to remove the venous cannulas you notice a stable but moderate-size haematoma in the region of the mid-portion of the coronary sinus.**

The most appropriate management of this problem is to

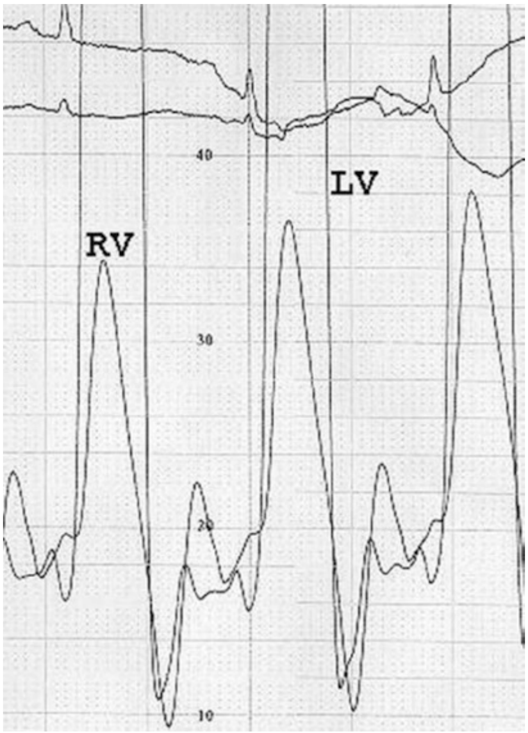
A. administer protamine, decannulate, complete the operation, and avoid manipulation of the involved area.
B. externally open up and explore the haematoma to patch the anticipated defect.
C. externally open up and explore the haematoma, then do a primary suture repair.
D. harvest another vein segment, dissect the haematoma, then ligate and bypass the injured vessel.
E. resume CPB and reopen the left atrium for inspection and possible intra-cardiac repair.

50. **A 69-year-old man has been treated medically for 3 years for progressive heart failure. Prior history includes CABG 4 years previously. Echocardiography shows an ejection fraction of 20%, LVEDD 7.5 cm, LESVI 160 mL/m^2, severe mitral regurgitation due to bileaflet tethering and moderate tricuspid regurgitation. Cardiac catheterization shows diffuse coronary artery disease bypass grafts to the anterior descending, diagonal, first obtuse marginal and posterior descending arteries are all patent. PA pressure is 58/25, PCW = 28, and CVP = 18.**

Which of the following best predicts that mitral valve repair will NOT provide sustained benefit for this patient?
A. Ejection fraction = 20%
B. LVEDD = 7.5 cm, LVESVI = 160 mL/m^2
C. Mean CVP = 18
D. PA pressure = 58/25
E. Patent coronary artery bypass grafts

51. **Cardiac resynchronization therapy is an appropriate therapy in which of the following patients?**
A. Fifty-eight-year old woman, non-ischemic cardiomyopathy, class IV heart failure, on chronic dobutamine, EF 15%, atrial fibrillation, with a QRS complex duration 135 ms
B. Sixty-three-year old woman, non-ischemic cardiomyopathy, class III heart failure on tailored therapy, EF 30%, third degree heart block with a QRS complex duration 115 ms
C. Sixty-five-year old man, hypertensive cardiomyopathy, class III heart failure on tailored therapy, EF 40%, sinus rhythm with right bundle branch block
D. Seventy-year old man, non-ischemic cardiomyopathy, class III heart failure on tailored therapy, EF 15%, atrial fibrillation with left bundle branch block
E. Seventy-two-year old woman, ischemic cardiomyopathy, class IV heart failure on tailored therapy, EF 15%, sinus rhythm with left bundle branch

52. **A 62-year-old man with rheumatoid arthritis presented with shortness of breath and lower extremity oedema. Physical exam revealed a positive Kussmaul's sign, marked jugular venous distension, and no significant pulsus paradoxus. Pressure tracings from his heart catheterization are shown. No coronary disease was present.**



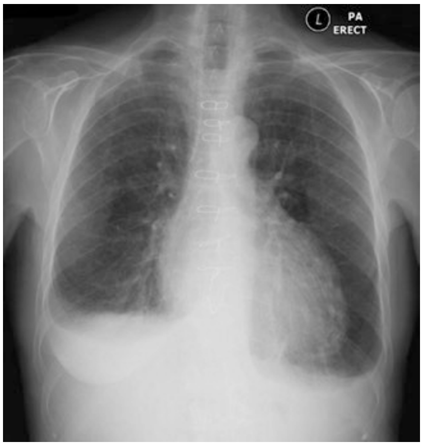
A. Constrictive pericarditis
B. Dilated cardiomyopathy
C. Pericardial tamponade
D. Restrictive cardiomyopathy
E. Tricuspid valve disease

53. **Because of severe heart failure symptoms a 71-year-old man has been taken to the operating room. Through a median sternotomy, a complete phrenic-to-phrenic pericardiectomy is underway for constriction. The left side dissection is complete but it is difficult to identify a tissue plane over the right side of the heart. Suddenly dark blood floods the operative field.**

The most appropriate management is
A. Application of topical sealants, direct pressure for 5 min, wide chest tube drainage and closure
B. Bovine pericardial patch repair using pledgeted sutures followed by chest closure
C. Felt strip repair of the right ventricular rent and completion pericardiectomy
D. Foley catheter placement through the injury, continued dissection and then primary closure
E. Institution of cardiopulmonary bypass, closure of the defect and completion pericardiectomy

54. **An 82-year-old woman underwent AVR with a bovine pericardial tissue valve 3 weeks ago. Her in-hospital postoperative course was uneventful. Three weeks**

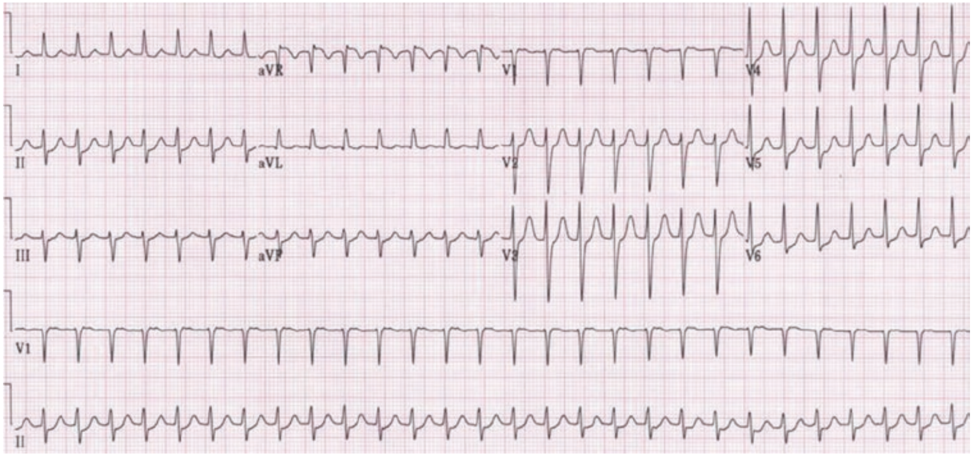
after surgery she was unable to lay supine and complained of severe shortness of breath with minimal exertion. She presented to the ER, where examination revealed no murmur, heart rate = 106, and BP = 92/55. The chest radiograph is shown.



The best treatment for this condition is

A. Anticoagulation for pulmonary embolus
B. Non-steroidal anti-inflammatory agents
C. Pericardial stripping
D. Pericardial window
E. Reoperation and placement of another valve

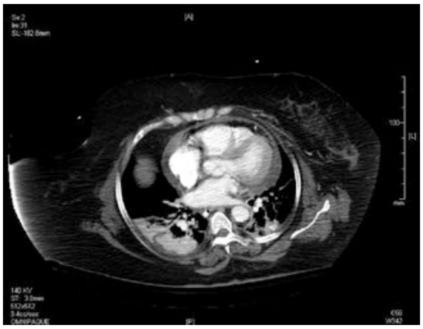
55. **A 54-year-old man with a normal ejection fraction underwent an uneventful 4-vessel CABG. On arrival in the ICU he was on no inotropes or vasopressors and cardiac output was 6 L/min. Mediastinal chest tube drainage was 175 mL/h for the first 3 h but diminished significantly thereafter. Six hours after surgery he developed a vasopressor requirement, which has been escalated to 10 μg/min of norepinephrine (noradrenaline). His cardiac output now is 3.1 L/min, CVP is 21 mmHg and urine output has diminished to 20 cc/h despite giving 1 L of IV saline. A stat ECG is shown.**



Which of the following is the most appropriate therapy?

A. 250 cc of 5% albumin
B. Cardiac catheterization
C. Epinephrine (adrenaline) at 2 μg/kg/min
D. Intra-aortic balloon pump
E. Mediastinal re-exploration

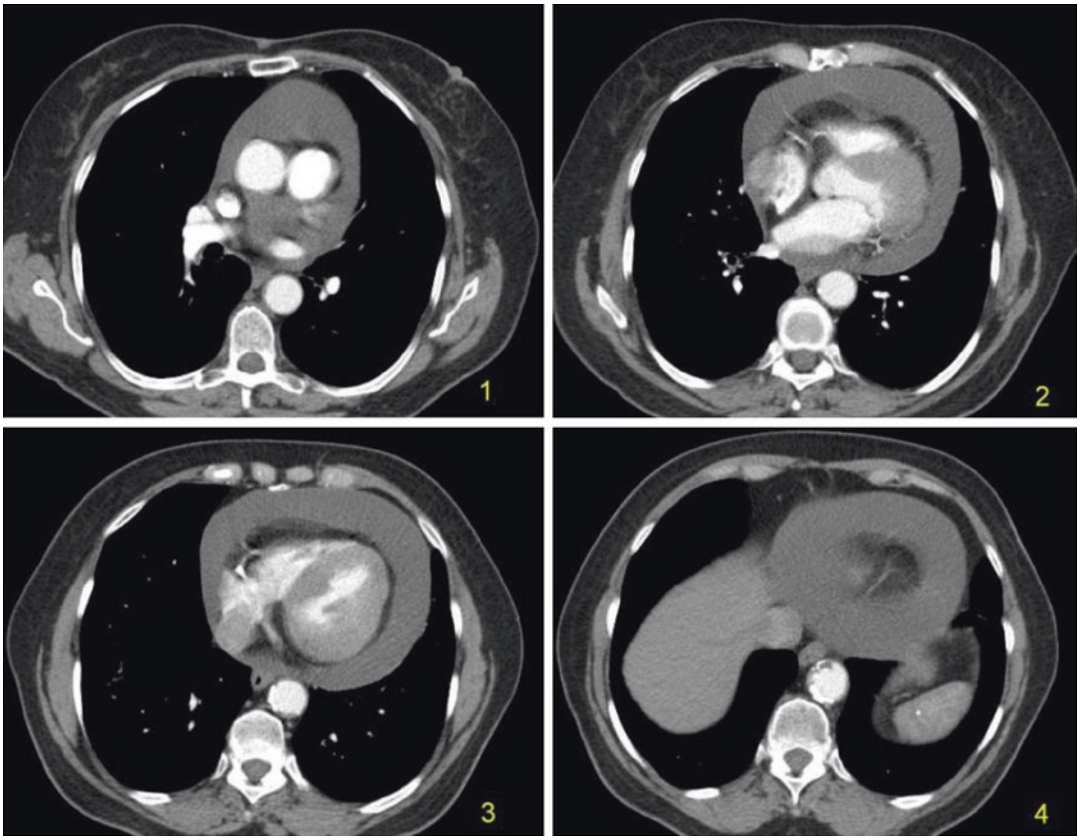
56. **An asymptomatic 42-year-old HIV positive woman had a chest CT study (see image).**



With respect to the pericardial abnormality displayed, which of the following statements is correct?

A. The abnormality typically becomes symptomatic with time.
B. Aggressive HAART therapy will expedite resorption.
C. Drainage is indicated to define the aetiology.
D. The aetiology is most probably fulminant CMV infection.
E. The finding marks a more advanced stage of HIV disease.

57. **A 75-year-old woman with a history of tobacco abuse presented with increasing shortness of breath and malaise. Contrast CT images are shown. Myocardial ischemia was ruled out and pericardiocentesis revealed no malignant cells.**



The most appropriate next step in the management is

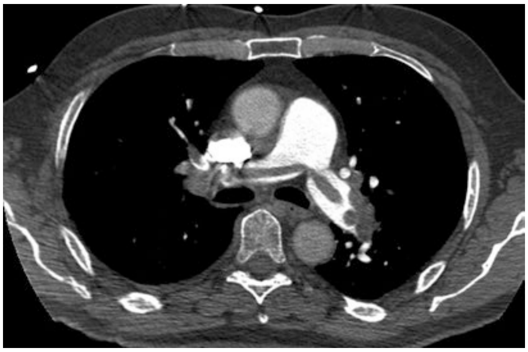
A. CT guided biopsy of the right upper lobe mass and definitive chemotherapy
B. Empirical antibiotic therapy with broad-spectrum antibiotic for 10 days
C. Median sternotomy and anterior pericardiectomy
D. Subxiphoid pericardial window with pericardial biopsy
E. VATS pericardial window with drainage into the pleural space and pleurodesis

58. **Eighteen months ago a 44-year-old woman completed 42 Gy of radiation therapy for mediastinal Hodgkin's lymphoma. She now complains of exertional dyspnea. Her chest radiographs have been clear, but a transthoracic echocardiogram showed normal ejection fraction, a moderate pericardial effusion and pericardial thickening. Five hundred milliliter of serous fluid was removed by pericardiocentesis but the patient's symptoms persist.**

Which of the following should be done next?

A. CT scan of the chest
B. Diuretic therapy
C. Exercise stress testing
D. A progressive exercise and conditioning regimen
E. Right heart catheterization

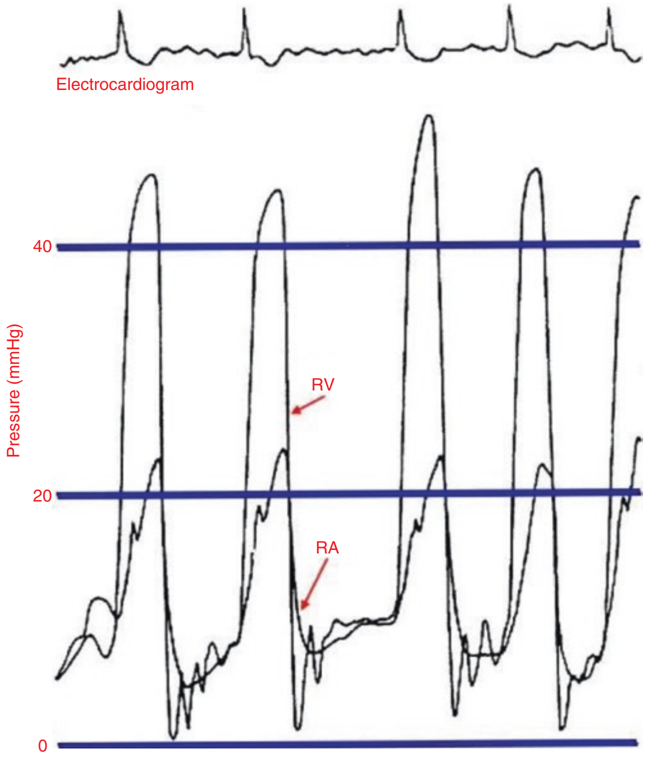
59. **A 51-year-old attorney with no significant past medical history was evaluated for complaints of shortness of breath, mild chest discomfort and fullness in his head after going for his morning walk. During stress testing in his cardiologist's office he had frequent PVCs and chest discomfort. A nitroglycerine drip was initiated, which caused hypotension and he was taken to the hospital. Coronary angiography showed no evidence of coronary artery disease, and he was discharged to home 2 days later with a diagnosis of pleurisy. The patient re-presented after a sudden collapse and hypotension required vasopressor support. Following intubation the chest CT was obtained.**



Which of the following is the most appropriate next step?

A. Heparinization and repeat left heart catheterization
B. Immediate operation for type A dissection
C. Endotracheal intubation and nitric oxide therapy
D. Lytic therapy for acute myocardial infarction
E. The procedure for which heart lung machine was invented

60. **A 75-year-old woman presented with a shortness of breath. The cardiac auscultatory exam was notable for an S3 that increased with inspiration and decreased with a Valsalva maneuver. Also heard was a parasternal pansystolic murmur that increased with inspiration. On physical exam, she had significant oedema. Right heart pressure tracings are shown (see figure).**



Which of the following operations should be offered to her based on this information?

A. Isolated tricuspid valvuloplasty
B. Mitral valve repair alone
C. Mitral valve repair and tricuspid valve repair
D. Mitral valve replacement and tricuspid valve replacement with bioprosthetic valves
E. Mitral valve replacement and tricuspid valve replacement with mechanical valves

61. **A 59-year-old woman has elevated 5-hydroxytryptamine (5-HT) serum levels and consequent systemic symptoms. Examination shows significant lower extremity oedema and ascites. A pansystolic murmur is heard over the left sternal edge. An echocardiogram of the tricuspid valve demonstrates fused commissures, thickened and fused chordae tendineae and combined regurgitation and stenosis.**

Of the following choices the most appropriate therapy is

A. Commissurotomy and repair with rigid ring
B. Intravenous broad spectrum antibiotics
C. Replacement with a bioprosthetic valve
D. Replacement with a mechanical valve
E. Valve excision without replacement

62. **A 42-year-old woman with shortness of breath and peripheral edema is scheduled for mitral valve repair (flail P2 resection and ring annuloplasty). PA pressure at catheterization was 56/18 and the preoperative echo showed moderate tricuspid regurgitation.**

The best treatment is to

A. Leave the tricuspid alone since the patient has only mild symptoms
B. Repair the tricuspid because the patient has a reduced ejection fraction
C. Repair the tricuspid because the patient has pulmonary hypertension
D. Replace the tricuspid valve because the annulus is dilated
E. Wait to decide until the intraoperative transesophageal echocardiogram is done

63. **A 54-year-old woman complains of fatigue and weakness. On physical exam, she has a parasternal pansystolic murmur that increases with inspiration. There is jugular venous distention with fused c- and v-waves followed by a prominent y-descent. A chest radiograph demonstrates cardiomegaly, increased right atrial and ventricular size and a prominent azygos vein.**

Echocardiography will most likely demonstrate

A. Mitral regurgitation
B. Mitral stenosis
C. Tricuspid regurgitation
D. Tricuspid stenosis and regurgitation
E. Tricuspid stenosis

64. **A 35-year-old intravenous drug user underwent excision of his tricuspid valve for endocarditis and intravenous antibiotic treatment of multiple small lung abcesses. Informed consent included an understanding that his chance of surviving 15 years was 63% and that most likely reason for his death would be**

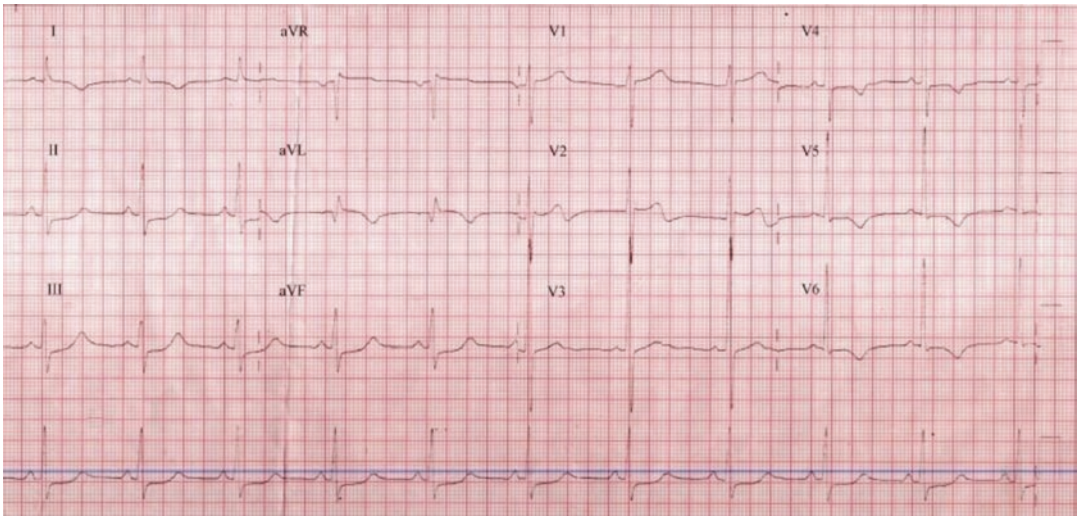
A. Coronary artery disease
B. Liver failure from right heart overload
C. Pulmonary embolism
D. Recurrent endocarditis
E. Return to drug addiction

65. **A 45-year-old woman is to undergo mitral valve repair for myxomatous disease. She has 4+ tricuspid regurgitation. The treatment that will give her the most sustained benefit for the right-sided pathology is**
    A. Annuloplasty with a near-complete rigid ring
    B. Annuloplasty with a partial flexible ring
    C. DeVega suture annuloplasty
    D. Mitral valve intervention only
    E. Tricuspid valve replacement

66. **A 60-year-old woman has ascites and peripheral oedema. In addition to a repairable prolapsing P2 mitral scallop, she has multiple chords ruptured on her tricuspid valve that preclude repair. She is in sinus rhythm.**

    Of the following, the best plan is to
    A. Repair the mitral valve and leave the tricuspid valve as it is
    B. Repair the mitral valve and place a bioprosthetic valve in the tricuspid position
    C. Repair the mitral valve and place a mechanical valve in the tricuspid position
    D. Replace the mitral and tricuspid valve with mechanical prostheses
    E. Replace the mitral with a bioprosthesis and place a mechanical valve in the tricuspid position

67. **A 73-year-old, 93 kg woman had severe aortic stenosis. Preoperative left ventricular function was normal, PA pressure was 50/23 and she had no obstructive coronary lesions. At operation the aortic annulus was too small to accept a 19 mm stented bioprosthesis, and aortic root reconstruction with a 21 mm porcine root was performed. Because of mild right ventricular dilatation, milrinone (0.5 μg/(kg min)) was used to wean from bypass. Frequent PVCs improved with a lidocaine infusion. TOE showed good valve function, LV ejection fraction of 55%, and no intracardiac air. Thirty minutes after arrival in the ICU, however, she had short runs of ventricular tachycardia, hypotension, and cardiac index dropped from 2.5 to 1.5 L/(min m^2). PA pressures are unchanged from the OR (40/20) and the milrinone and lidocaine infusions are checked and found to be running. The ECG is shown. The chest film is unremarkable and the arterial blood gas values are: pH 7.35, pCO_2 41 mmHg, pO_2 245 mmHg, HCO_3 21 mEq/L.**



    Which of the following is the most important management strategy?
    A. Amiodarone 150 mg IV followed by infusion.
    B. Discontinue milrinone and begin adrenaline at 2 μg/min.
    C. Increase the ventilator rate from 14 to 18 breaths per minute.
    D. Place an intra-aortic balloon pump at the bed side.
    E. Return to the OR for aortocoronary bypass grafting.

68. **A 57-year-old obese man underwent minimally invasive aortic valve replacement via partial upper sternotomy. The inferior rim of his left main coronary ostium was noted to be 11 mm above the aortic annulus. On POD#4, he developed atrial fibrillation and blood pressure was labile. Beta blockers and amiodarone converted the rhythm to normal sinus but his blood pressure now continues to be labile. Urine output is 20 cc/h and creatinine (normal before surgery) is 1.7. His wound is shown. Neck veins are hard to**

evaluate, but he has 2+ pretibial edema bilaterally. He says he feels fine.

Which of the following should be done?

A. Give furosemide to increase urine output.
B. Obtain a chest CT to rule out dissection.
C. Obtain a precordial echocardiogram.
D. Request an urgent coronary angiogram.
E. Start a dopamine drip and get a chest radiograph.

69. **An 82-year-old man who was otherwise healthy underwent aortic valve replacement with a porcine prosthesis for critical, symptomatic aortic stenosis. His operation was uncomplicated and the postoperative echocardiogram demonstrated a well-seated valve without dysfunction. The evening of surgery (8 h after leaving the operating room) the nurse reported that he was unable to move the entire right side of his body. He was completely awake and responsive. A non-contrast brain CT scan was unremarkable. Optimal management should include**

A. anticoagulation and alpha agonist administration.
B. bedside duplex of lower extremity veins.
C. cerebral angiography with catheter-directed, intra-arterial thrombolysis.
D. immediate transport to hyperbaric oxygen chamber.
E. intravenous thrombolytic therapy.

70. **A 3 year old child is noted to have a murmur of aortic stenosis. Cardiac catheterization demonstrates a peak-to-peak left ventricular-to-aortic gradient of 50 mmHg, mild aortic regurgitation, and the echocardiogram shows a circumferential fibrous ridge in the left ventricular outflow tract. Proper management is**

A. aortoventriculoplasty (Konno' procedure).
B. continued close follow-up until the gradient increases further or symptoms appear.
C. open aortic valvotomy.
D. percutaneous balloon dilatation.
E. transaortic resection.

71. **The aortogram of a symptomatic 10 year old child with Williams syndrome shows supravalvular aortic stenosis. Of the following procedures, appropriate management is**

A. composite aortic root replacement.
B. Dacron graft replacement of ascending aorta.
C. open valvotomy on bypass.
D. patch enlargement of the aorta.
E. percutaneous balloon dilatation of the aortic valve.

72. **A 6 year old patient underwent closure of a secundum atrial septal defect. At operation a persistent left superior vena cava was noted which was separately cannulated for bypass. The atrial septal defect was closed with a pericardia! patch. Upon weaning from bypass, systemic arterial desaturation is noted. A likely cause is unrecognized**

A. anomalous hepatic venous drainage.
B. anomalous pulmonary venous drainage into the right superior vena cava.
C. coronary sinus septal defect.
D. pulmonary valve stenosis.
E. ventricular septal defect.

73. **During intracardiac repair of a complete atrioventricular septal defect there is an excessive amount of blood streaming from the left atrium. The most likely cause of this is**

A. anomalous origin of the left coronary artery from the pulmonary artery.
B. azygous continuation of the inferior vena cava.
C. partial anomalous pulmonary venous connection.
D. a patent ductus arteriosus.
E. a patent left superior vena cava to the coronary sinus.

74. **The most likely cause of a poor long-term result following surgical repair of a complete atrioventricular septal defect is**

A. left ventricular outflow tract obstruction.
B. mitral valve regurgitation.
C. pulmonary vascular obstructive disease.
D. residual atrial septal defect.
E. residual ventricular septal defect.

75. **The most common late complication after an arterial switch operation for transposition of the great arteries is**

A. atrial arrhythmias.
B. coronary ostial stenosis.
C. pulmonary artery stenosis.
D. recanalization of the ductus arteriosus.
E. stenosis of the aortic anastomosis.

76. **The arterial switch operation is optimally performed in the first 2 weeks of life for patients with transposition of the great arteries and intact ventricular septum because the**

A. atrial septal defect created by balloon septostomy is likely to close and cause lethal hypoxemia.
B. left ventricle is still physiologically prepared to function as a systemic ventricle.
C. older newborn is a poorer surgical candidate.
D. right ventricle is physiologically prepared to eject against elevated neonatal pulmonary vascular resistance.
E. use of prostaglandins for longer than 2 weeks is contraindicated.

77. **A 2 month old patient with atresia of the tricuspid valve, ventricular septal defect, normally related great vessels, and no pulmonary stenosis will benefit most from which of the following surgical interventions?**

A. patch closure of an atrial septal defect
B. patch closure of a ventricular septal defect

   C. patch closure of both the atrial and ventricular septal defects
   D. pulmonary artery banding
   E. systemic-to-pulmonary artery shunt

78. **The best initial diagnostic studies for a 4 month old infant with stridor since birth are**
   A. angiography and barium swallow.
   B. chest X-ray and angiography.
   C. chest X-ray and barium swallow.
   D. computed tomography and angiography.
   E. magnetic resonance imaging and computed tomography.

79. **The most important reason for cardiac catheterization in the preoperative evaluation of a 2 year old child with a ventricular septal defect (VSD) is to determine**
   A. coronary artery anatomy.
   B. if additional VSDs exist.
   C. location of the VSD.
   D. pulmonary vascular resistance.
   E. relationship of the VSD to the tricuspid valve.

80. **A 4 year old asymptomatic child has the following data recorded at cardiac catheterization**

	Pressures (mmHg)	% Saturation
SVC	2	55
RA	2	57
IVC	2	60
RV	50/2	85
PA	52/26 (38 mean)	85
LA	2	100
LV	125/4	100
AO	125/82 (98 mean)	100

The Qp/Qs (ratio of pulmonary to systemic blood flow) is
   A. 0.5
   B. 1.0
   C. 1.5
   D. 2.0
   E. 3.0

81. **A 1-week-old neonate with transposition of the great arteries, ventricular septal defect, and coarctation of the aorta underwent a primary one-stage correction through a median sternotomy. Despite maximal inotropic support, the baby cannot be weaned from cardiopulmonary bypass. Transesophageal echocardiography reveals biventricular dysfunction and a technically satisfactory repair with flow in both coronary arteries. Which of the following forms of mechanical support represents the best option for this patient?**
   A. intra-aortic balloon pump via aortic arch
   B. veno-arterial ECMO via existing right atrial and aortic cannulas
   C. veno-arterial ECMO via femoral vein and femoral artery
   D. veno-venous ECMO via jugular vein
   E. ventricular assist device (VAD) without oxygenator via existing right atrial and aortic cannulas

82. **A 16-year-old patient underwent an atrio-pulmonary type Fontan procedure for tricuspid atresia at age 2. She now complains of worsening exercise tolerance. The late complication that is most likely to cause her symptom is:**
   A. left ventricular failure
   B. pleural effusion
   C. protein-losing enteropathy
   D. right ventricular failure
   E. supraventricular arrhythmia

83. **A 5-year-old girl had neonatal repair of truncus arteriosus with a right ventricle-to-pulmonary artery homograft conduit. She developed progressive exercise intolerance and echocardiography indicated conduit stenosis. She underwent cardiac catheterization and balloon dilation of the conduit valve. Which of the following findings is an indication for conduit valve replacement?**
   A. heavily calcified conduit
   B. pulmonary valve regurgitation
   C. right ventricular end-diastolic pressure = 10 mmHg
   D. right ventricular hypertrophy
   E. right ventricular pressure = 80% of systemic pressure

84. **A 17-year-old man is found to have a restrictive ventricular septal defect with a sinus of Valsalva aneurysm of the non-coronary sinus. Rupture of this aneurysm would most likely result in an aortic fistula to:**
   A. left atrium
   B. left ventricle
   C. pericardial sac
   D. right atrium
   E. right ventricle

85. **A 3-year-old boy born with tricuspid atresia was initially palliated with a right modified Blalock-Taussig shunt. At age 9 months he underwent shunt takedown and a bidirectional Glenn (cavopulmonary anastomosis) procedure. Which of the following would significantly increase his risk for a lateral tunnel Fontan procedure?**
   A. central pulmonary artery stenosis
   B. interrupted inferior vena cava with azygous continuation
   C. left ventricular end-diastolic pressure = 16 mmHg
   D. systolic pulmonary artery pressure = 16 mmHg
   E. transpulmonary gradient = 6 mmHg

Answers

1. **Answer: C**

   In the Arterial Revascularization Trial (ART), patients were randomly assigned to receive either bilateral internal thoracic artery grafts or a standard single left internal thoracic artery graft during coronary artery bypass grafting (CABG). A prespecified interim analysis at 5 years showed no significant differences between the two strategies with regard to all-cause mortality or the rate of the composite outcome of death from any cause, myocardial infarction, or stroke. At 10 years, in intention-to-treat analyses, there were no significant between-group differences in all-cause mortality; in the rate of the composite outcome of death, myocardial infarction, or stroke; or in the rate of repeat revascularization.
2. **Answer: A**

   Problems that arise after uneventful operations can be frustrating, yet a thoughtful approach to diagnosis and prompt management can be lifesaving. Emergent cardiac catheterization in a postoperative patient with new onset ventricular arrhythmias may be indicated, but several factors make coronary disease unlikely in this case. No native occlusive lesions were identified at preoperative catheterization. With the aorta open, return of retrograde cardioplegia from both coronary ostia would have been visualized. Unnoticed coronary injury is unlikely, and obstruction by debris would have manifested intraoperatively with ventricular dysfunction and difficultly weaning from cardiopulmonary bypass. In this scenario, the most likely cause is air embolism from small air bubbles trapped in the pulmonary veins, the left atrium or the left ventricle after an open operation. This problem can occur despite aggressive de-airing and the use of transesophageal echo. In a supine patient the right coronary ostium is superior in the ascending aorta and is, therefore, the most common site of coronary air embolism. Air embolism into the carotid circulation can cause early postoperative seizures. Ambient air (80% nitrogen) is absorbed into solution much more slowly than pure oxygen or CO_2. For this reason insufflation of the pericardial well during operation with CO_2 is routinely practiced by many surgeons. Anticonvulsant medications are indicated and obtaining a CT scan emergently is reasonable for a stable patient, but a neurosurgical problem such as an acute bleed is unlikely in this situation. Hyperbaric oxygen is an appropriate treatment to help clear nitrogen-rich gas bubbles, but chambers are seldom available and postoperative cardiac patients are not easily transported or cared for in such microenvironments. Fortunately, most air embolism complications are self-limited problems and injury can be minimized by employing brute force (increasing cardiac output and systemic pressure) to purge the obstructing gas bubbles. Induced moderate hypothermia will minimize the metabolic demands of the heart and brain until the problem is resolved.
3. **Answer: C**

   A bicuspid aortic valve (BAV) is a recognized risk factor for the development aneurysms of the ascending aorta and subsequent complications such as dissection or rupture. BAV disease seems to follow an autosomal dominant pattern of inheritance with incomplete penetrance. A number of histologic abnormalities have been identified in association with BAV including decreased fibrillin 1 concentration, increased metalloproteinase 2 activity, elastin fragmentation and smooth muscle cell reorientation. Distances between elastic lamellae are greater than in patients with tricuspid aortic valves. Subsequently, these patients also have higher rates of dilation of the ascending aorta on long-term echo surveillance than do patients with tricuspid valves.

   A patient with a BAV and ascending aortic diameter greater than 45 mm is at increased risk of late aortic dissection and sudden death compared to patients with smaller aortic diameters. Reconstruction of the entire aortic root and ascending aorta with a composite graft should be considered if the aortic root is also dilated. The increased complexity and operative risk of a Bentall procedure mitigate against its routine use in patients without coexistent root dilatation. Replacement of the ascending aorta with a tube graft in addition to valve replacement or repair is an appropriate procedure in the absence of root enlargement. Reduction aortoplasty with external wrapping of the ascending aorta has been reported to have acceptable mid-term results, but

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long-term follow-up suggests an increased incidence of progressive dilatation in comparison to tube graft replacement of the ascending aorta.

4. **Answer: E**

   Paravalvular leak occurs in approximately 1–3.4% of patients after aortic valve replacement. Factors implicated in the development of periprosthetic leaks include inadequate debridement of annular calcium, endocarditis, using non-pledgeted annular sutures, and anatomic weakness in the area of the non-coronary sinus. Indications for intervention include regurgitation worse than "mild," worsening ventricular function, hemolysis, and endocarditis. "*Vena contracta*" refers to the point in a fluid stream through an orifice where the diameter of the stream is the least. In the case of a paravalvular leak the abnormal fluid stream can be imaged and measured by echo techniques. The maximum contraction is usually identified slightly downstream from the orifice. A regurgitant jet *vena contracta* of 0.6 cm indicates moderate to severe regurgitation, which is consistent with this patient's postoperative ejection fraction deterioration. Percutaneous closure of prosthetic paravalvular leaks is an appealing alternative to reoperation, but embolization, hemolysis and lack of successful complete closure have plagued such attempts. The devices used in reported cases have been designed for other purposes to resolve lesions such as muscular VSD, ASD, and PDA. Reoperation is the conservative and only reliable approach to resolve the complication described. The simplest repair technique, when anatomically feasible, is to close the defect with one or more transmural pledgeted sutures that incorporate the sewing ring and the aortic wall. In the noncoronary sinus sutures can be placed from outside-to-inside and up through the sewing ring at the level of the annulus. Leaks in other paravalvular locations can be more difficult to resolve, but further dissection and alternate exposures may allow similar transmural suture repair in the left and right coronary sinuses. Prosthetic valve re-replacement may be required, but this is associated with reduced postoperative survival.

5. **Answer: D**

   Identification of moderate aortic stenosis at the time of myocardial revascularization presents a clinical dilemma. Concomitant valve replacement poses and increased operative risk, but the stenosis may progress and require a reoperation later, when risks are even higher. Aortic stenosis is a progressive disease process with a long latent period in which patients may be asymptomatic. Once symptoms do develop, the risks progress exponentially to death unless the obstruction is removed by valve replacement. The natural history of asymptomatic carotid stenosis is relatively benign, and surveillance plus antiplatelet drugs are recommended for nearly all such patients. Combined carotid endarterectomy and CABG may be appropriate for selected patients with high-grade carotid lesions. Recent studies offer some insights into which patients can be expected to have accelerated progression of aortic stenosis. Valve obstruction correlates with valvular calcification. Therefore, valves with moderate stenosis and heavy calcification of the annulus and leaflets tend to worsen and cause symptoms sooner than valves with minimal calcification. Additionally, the starting valve area is related to the interval time to symptom development. Studies of aortic stenosis have shown an annual decrease in aortic valve area of approximately 0.12 cm^2/year and an increase in mean gradient of 5–10 mmHg/year. Some authors suggest that this progression is more rapid in elderly patients. Regarding the described patient, the calcification and moderate gradient indicate that failure to replace the aortic valve at this time puts him at high risk for a required second operation within a few years. The potential role of transcatheter valve insertion in this setting remains to be defined.

6. **Answer: D**

   Reoperative bypass surgery is becoming less common with increased application of percutaneous revascularization. Before IMA advantages were generally accepted, LAD revascularization was routinely done with a saphenous vein graft. If reoperation is necessary, use of the LIMA would appear to be an attractive option. However, its use in this context can result in marginal LAD perfusion prior to full maturation of the arterial graft. When a saphenous vein graft was previously placed to the LAD acceptable reoperative strategies include either replacing the old graft with a new saphenous vein graft (removing or ligating the old graft), or placing a LIMA to the LAD and leaving the old graft intact. This woman's old patent LAD vein graft was ligated, so the LIMA inflow is now the sole source of anterior wall perfusion. Noninvasive determination of LIMA flow is reliable, and if no technical error was made then going back on bypass to redo the LIMA-LAD anastomosis will not resolve the ongoing ischemia, which is the underlying problem in the described scenario. The measured flows are reasonable values for fresh grafts of the types specified. Augmenting anterior wall flow is the appropriate immediate response. Placing an intra-aortic balloon pump and adding inotropic support may temporize the situation, but the underlying cause remains untreated. LVAD placement fails to address the pathophysiology and is premature. If another graft fails to resolve the problem, then embolized debris from old graft manipulation and/or other etiologies must be considered, and extraordinary circulatory support may be justified.

7. **Answer: D**

    Most authorities recommend repair of the mitral or tricuspid valve in any patient with severe regurgitation of either valve. The American College of Cardiology and American Heart Association (ACC/AHA) guidelines recommend repair for severe ischemic mitral regurgitation or severe tricuspid regurgitation at the time of concomitant coronary bypass or other surgery. Severe pulmonary hypertension and poor left ventricular function are each associated with persistent or progressive postoperative tricuspid regurgitation (even after repair), so many surgeons advocate an aggressive strategy to correct even lesser degrees of tricuspid regurgitation. The severity of ischemic mitral regurgitation or functional tricuspid regurgitation is highly dependent on preload, afterload and ventricular function. Fasting and sedation under general anesthesia may result in substantial down-grading of mitral or tricuspid regurgitation when assessed in the operating room. The preoperative echo assessment under normal loading conditions offers the most accurate assessment of atrio-ventricular valve regurgitation. An aggressive plan for CABG plus mital and tricuspid repairs is correct. Excellent results have been reported for repair of ischemic mitral valve regurgitation with flexible, rigid and semi-rigid rings. The best mid-term results of survival and freedom form recurrent ischemic mitral regurgitation have been reported with semi-rigid annuloplasty rings. Regardless of the type of ring used, after 1 year there appears to be no difference in annular motion or basal contraction after mitral annuloplasty. The posterior annulus is the perimeter of the tricuspid valve most prone to dilatation. The primary role of a tricuspid annuloplasty ring is to correct dilatation of the posterior, and to a lesser extent the anterior, annulus. Most modern tricuspid "rings" are not complete rings, but partial with a gap to minimize the risk of damage to conduction system. The atrioventricular node and penetrating bundle of His are close to the septal leaflet base and the commissure between the septal and anterior leaflets. The anatomy of the valve and the triangle of Koch are seen in the second figure (forceps tips are in the coronary sinus). The apex of this triangle corresponds to the area of most concern for injury from suture placement.

8. **Answer: E**

    This woman's echocardiogram shows a large anterior effusion with diastolic RV collapse and impaired LV function with posterior akinesis. Postinfarction free wall ventricular rupture is most frequently seen in hypertensive women over age 60. Signs and symptoms of cardiac tamponade, heart failure and shock are most often seen. Ventricular rupture represents a surgical emergency, although patients may be stabilized temporarily with pericardiocentesis and placement of an intra-aortic balloon pump. Catheterization is not mandatory. In the pre-thrombolytic era this complication of myocardial infarction presented within 2 weeks of the initial infarct (peak at 5 days). However in the current era ventricular rupture can develop within hours of thrombolysis or reperfusion. Emergent operation for this problem can be technically challenging, but it may be further complicated by bleeding secondary to the drugs given. Like postinfarction ventricular pseudoaneurysm and papillary muscle rupture, free wall rupture tends to be the result of acute single-vessel coronary occlusion in the absence of developed collaterals. The size of the area of infarction is often relatively limited and concomitant procedures are seldom necessary. Surgical treatment may include: (1) wide pledgeted closure of the rupture (often difficult because of friable tissue); (2) infarctectomy with patch closure of the defect; (3) pledgeted closure of the rupture with a wide Dacron patch sewn to good tissue and placed over the repair as a second layer; and (4) direct application of a patch glued over the infarct, done off-pump if possible. The last of these options has persuasive advantages. Fibrin glue is inadequate for reliable adhesion and strength, but gelatin resorcin formaldehyde glue has been used effectively. Various cyanoacrylate synthetic glues have convincing strength and proven efficacy, and the nature of the patch material seems less critical when these adhesives are used.

9. **Answer: D**

    Some variety of myocardial rupture (free wall, septal, or papillary muscle) complicates up to 10% of all acute myocardial infarctions (AMI) and is responsible for 15% of in-hospital mortality following AMI. Reports indicate that early reperfusion for coronary disease (either PCI or CABG) minimizes such complications. Myocardial rupture is more common among patients older than 60 years and women as compared to men (1.4:1). Most myocardial ruptures occur between 1 and 5 days following AMI. Echocardiography offers rapid, accurate diagnosis of these conditions. In the described case the findings were near-complete papillary muscle rupture, which can manifest as acute pulmonary edema with associated tachycardia, tachypnea, rales, respiratory distress, and hypotension. In roughly 2/3 of cases of acute papillary muscle rupture the posteromedial papillary muscle is involved. The posteromedial papillary muscle usually receives blood supply from a single source—either the right coronary artery or the circumflex coronary artery in a left dominant system. The anterolateral papillary muscle receives dual blood supply from the left anterior descending and circumflex coronary arteries. The presentation of acute MR represents only 1–2% of all cases of ischemic MR. Rapid diagnosis is essential to survival. A murmur may be absent following papillary muscle rupture given a rapid equalization of pressure between the left atrium and ventricle. "Medical" therapy includes afterload reduction with vasodilators and/or insertion of an intra-aortic balloon pump. However, often these patients develop acute, severe cardiogenic shock that is unresponsive to inotropic and IABP support. Mitral valve replacement is the best surgical option in most cases. It is associated with 10–40% mortality depending on patient comorbidities, but without valve replacement this condition is fatal.

10. **Answer: B**

    Ten-year survival for asymptomatic patients with LV aneurysms is 90%. Therefore, surgical intervention should not be undertaken based on the presence of an aneurysm alone. Aneurysm resection is not beneficial for asymptomatic patients with large (>5 cm) aneurysms. Indications for surgery include documented increase in size of the aneurysm, angina, congestive heart failure symptoms, arrhythmias, rupture, and peripheral embolism. Eight-five percent of LV aneurysms are anterior, as the left anterior descending coronary artery is the most commonly involved vessel. The LAD should be bypassed at the time of aneurysm repair. The most significant factor influencing postoperative mortality is poor left ventricular function before operation. Other factors that predict post-repair mortality include three-vessel disease, preoperative malignant arrhythmias, and advanced age. "Circular" repair (Dor, Jatene, others) is generally favored over linear closure, but the influence on outcome of the method of repair remains somewhat controversial. Ejection fraction will improve following repair for almost all patients. However, primary heart transplantation should be considered if the ejection fraction is less than 20%, if symptoms are NYHA class IV, and if the patient is a good candidate for transplantation. The causes of death for medically managed patient are: arrhythmia (44%), heart failure (33%), and recurrent MI (11%).

11. **Answer: E**

    Fortunately, the need for post-cardiotomy ventricular assistance in patients with reasonable preoperative function appears to have decreased because of improved myocardial protection strategies. However, the relative number of patients with poor preoperative cardiac function has risen and thus the need for unexpected post-cardiotomy support remains essential. The most effective strategy to deal with this scenario is early institution of ventricular support prior to end-organ damage. This requires considerable judgment, experience with device options and dogged attention to care details. Creating and following guidelines and established protocols for institution of extraordinary mechanical ventricular support (beyond inotropes and/or intra-aortic balloon pump) improve survival dramatically. Samuels et al. showed that early (within 3 h) institution of VAD support once two or more high-dose inotropes are required produced improved survival. Several current ventricular support devices are readily available and can be inserted without extensive previous experience. The described patient has profound left ventricular failure and ample evidence of inadequate systemic perfusion. Correcting the acidosis may optimize the response to pharmacologic support, but the underlying muscle dysfunction is global and severe. The man's pulmonary hypertension is a reflection of left ventricular failure, and response to nitric oxide is unlikely. Functional grafts are documented, so additional bypass conduits are not indicated. Contractility will not return quickly and aggressive inotropic stimulation will worsen the chance of recovery. Venoarterial ECMO is an option, but it is not necessary if mechanical support is instituted early enough to prevent lung damage. Isolated LVAD placement will probably suffice for univentricular failure, although occasionally biventricular support becomes necessary. Failure to institute extended mechanical support early in a patient such as this inevitably leads to morbidity, failure to wean from VAD support, and ultimate mortality.

12. **Answer: E**

    This man had multiple pre-existing problems and underwent three on-pump procedures within 48 h. He was intubated, profoundly coagulopathic, in worsening acute renal failure, and grossly volume overloaded. His large antero-apical infarction makes the anastomosis of the LVAD inflow cuff difficult. Nonetheless, bleeding from this anastomosis is unlikely because the left ventricle is well decompressed by the LVAD. The low intraventricular pressure plus protamine and blood component transfusions control this bleeding. Similarly, with proper technique bleeding from the outflow graft anastomosis should not be problematic. The patient's renal dysfunction will likely develop into post-LVAD renal failure and require continuous venovenous hemodialysis (CVVHD). In the past, renal failure was single most powerful predictor of post-LVAD mortality during device support. Aggressive, early institution of CVVDH with adequate circulation from VAD support will likely lead to recovery of renal function. Liver failure often adds to multi-system organ failure in chronic end-stage heart failure cases, but once acceptable hemodynamics are restored, hepatic function will recover. This patient also appears destined to have worsening right ventricular function. Volume overload is evident from the high CVP but PA pressure elevation is modest. Despite the previous

LVAD the patient's right heart is failing, a secondary complication that develops in approximately one third of LVAD implants. A BiVAD strategy is probably necessary, as RV failure following LVAD alone results in 40–50% mortality before successful bridge to transplantation.

13. **Answer: A**

    Bleeding is the most common complication associated with LVAD implantation. Excessive bleeding (>4 units) occurs in most patients, and returning to the operating room for control is frequent (up to 60%). Preoperative comorbidities such as renal insufficiency, hepatic congestion, and low flow state contribute to the high incidence of bleeding. Strategies to manage coagulopathy include preoperative Vitamin K, preoperative plasmapheresis, priming the cardiopulmonary bypass circuit with fresh frozen plasma, and use of antifibrinolytics. Some surgeons routinely perform delayed chest closure so tamponade and emergency reoperation can be avoided. Planned, early post-pump treatment of coagulopathy with FFP, cryoprecipitate and platelet transfusions is routine in many centers. Recombinant factor VII has been used effectively both intra- and postoperatively in VAD patients, but several reports caution against routine use of this drug and component therapy because of potential pro-thrombotic consequences. After LVAD placement the reported rates of stroke and thromboembolism vary from 10% to 30%. The type of device, anticoagulation regimen, and various definitions of "neurological event" each influence statistical reports of these complications. Excessive transfusion of blood products is associated with several postoperative complications, including right ventricular (RV) failure, which is reported to occur in up to 30% of patients who require an LVAD. RV function in the initial postoperative phase often determines mortality after LVAD. A typical LVAD patient requires one or two inotropes and either inhaled nitric oxide or prostacyclin to achieve and maintain adequate LVAD flows. All agents usually can be weaned off slowly over a few days. Despite this anticipated outcome, a right-side VAD is required in approximately 10% of LVAD patients. The incidence of RVAD use has not been higher with the use of newer generation rotary pumps. Outcome reports indicate similar results for nearly all bridge LVAD devices, with survival to transplantation in 60–70% of patients and survival to discharge after transplantation of 50–60% of the total population. For comparison, 84% of non-bridged listed patients receive a transplant (UNOS, 2008; USA patients 07/01/2004–12/31/2006). Despite increased immunologic sensitization in bridged patients, contemporary post-transplant survival is similar to non-bridged patients, which is 85–90%. Overall infectious complications are less with continuous flow VADs. Bacteremia (25%) and pump endocarditis (3%) are equivalent. However, driveline, pocket, wound, and local device infections and sepsis are all substantially lower with axial flow devices.

14. **Answer: D**

    The patient is an obese young man with blood type O who has failed medical management despite several admissions and good outpatient compliance. Studies have shown that repeated hospitalizations for fluid overload are generally associated with high mortality. The recent development of ventricular tachyarrhythmia makes inotropic therapy dangerous, even with an ICD in place. This patient failed his pulmonary vasodilator challenge, so a plan to use milrinone in the hopes of lowering pulmonary vascular resistance is futile. With his demonstrated irreversible pulmonary hypertension (PVR > 4 Woods units, TPG > 15 mmHg) the risk of acute right heart failure following a heart transplant is considerable, and is associated with elevated short- and long-term mortality.

    This patient's weight and blood type each portend a long waiting time for an appropriate donor heart. Noting the recent ventricular arrhythmias in the setting of high pulmonary vascular resistance, mechanical support is needed. Despite the lack of response to nitroprusside and milrinone, the refractory high PVR is probably not absolutely "fixed" in this young adult. Volume and pressure unloading by an LVAD will improve systemic output and should progressively decrease pulmonary vascular resistance, thus reversing a contraindication to transplantation.

15. **Answer: E**

    Right heart function must be accurately assessed during patient evaluation for destination therapy (DT). All DT at present involves placing an isolated left-sided mechanical device. Hence, long-term success requires adequate right ventricular (RV) function. Although there are no firm guidelines that assure RV function, current workup includes a hemodynamic profile and echocardiography. Low pulmonary artery pressure, low RV stroke work index (RVSWI) and several other parameters have been associated with RV failure after LVAD placement. A right ventricular "risk score" based on preoperative clinical, laboratory, echocardiographic, and hemodynamics may be used to predict post-LVAD RV failure. Catheterization is mandatory in this patient to gather pressure data and to evaluate the posterior descending artery graft. If the conduit supplies a large territory of the RV then it must be preserved or regrafted. This patient's mechanical valve is a significant issue. Diverting flow with an LVAD will lead to stasis and the prosthetic valve will clot. If the valve then opens periodically, the risk of thromboembolization is quite high. This complication must be prevented, although adding an aortic valve procedure may increase the morbidity and mortality of LVAD placement. This does not, however, prohibit destination LVAD placement. Replacement of the existing mechanical valve with a bioprosthesis adds to the cross clamp time, and this does not prohibit ejection and the thromboembolic risk. The best strategy is to close the prosthetic valve with a prosthetic patch or immobilizing suture through an aortotomy. The disadvantage of this strategy is that if the LVAD fails, there will be no cardiac output and mortality is certain.

16. **Answer: A**

Patients with acute myocardial infarction who have failed percutaneous angioplasty and undergo emergent CABG surgery are at high risk for postcardiotomy shock. Delayed reperfusion can be deleterious and it is unclear how much myocardium is salvageable. The incidence of post-cardiotomy shock is 0.2–0.5 % of all patients who undergo cardiac surgery. Unfortunately, survival to recovery remains poor, reported to be 20–40% even in recent studies. Strategies that have shown improved survival have generally involved early application of mechanical support and transitioning to chronic LVAD or BiVAD support if necessary. In the case discussed above the patient is not a candidate for destination therapy, which is approved only for chronic heart failure. Furthermore, adding another complicated operation in this setting almost certainly invites further complications. The simplest available option to establish adequate temporary support is often best. While a percutaneous device with left atrial cannulation achieved through the atrial septum is a possibility for left-side support, many cases of postcardiotomy shock require biventricular support. This patient's recent MI involved the right coronary, so biventricular failure is almost certain. ECMO or short-term mechanical ventricles or blood pumps should be used in this case, with specifics determined by availability and expertise of the surgical team involved. Cannulation schemes for RV support should be the right atrial appendage with an outflow graft to the pulmonary artery or by cannulating through the RV outflow tract. Cannulation for the left side most commonly involves LA through the interatrial groove or the right superior pulmonary vein, with return to the aorta through direct cannulation or a graft. However, many experienced surgeons advocate direct cannulation of the LV apex to allow for maximal decompression of the left ventricle, fewer cannula complications and higher VAD flows, and improved chance for recovery.

17. **Answer: D**

The pattern of coronary blood flow during the coronary cycle is unique. Epicardial coronary vessels serve as capacitance vessels, primarily filling during the period of diastole (as much as 85% of total flow), and intramural pressure and resistance to myocardial perfusion progressively increase from the outer to inner layers of the heart. Myocardial arterioles have tremendous vasodilatory reserve capacity and enable high flow with low resistance in response to exercise. Two mechanisms of vasodilatation may be available: larger proximal vessels by endothelium-derived nitric oxide, and direct stimulation of smooth muscle cell alpha2-receptors by adenosine and other metabolites.

A coronary artery with an oblique origin, an intramural (within the wall of the aorta) course, or a position between the great arteries (as seen in this patient's CT) may be compressed and its reservoir capacity may be severely limited. The law of Laplace (tension = pressure × radius) dictates that comparable pressure in larger vessels creates greater wall tension. Thus the aorta and main pulmonary artery can compress smaller vessels that course between them or are intramural. Signs and symptoms in older patients can include angina, syncope, arrhythmias, MI, enlarged heart, and sudden death, which is most often associated with activity. Sudden death is frequently observed in association with anomalous origin of the left coronary artery from the right sinus of Valsalva. This pattern is associated with an oblique origin, a slit-like ostium, and an intramural, inter-arterial course. Each of these features (oblique origin, ostial stenosis, intramural and intra-arterial compression) can diminish flow and result in coronary ischemia. Limited flow and loss of reservoir capacity cannot meet the increased myocardial oxygen demands associated with exercise.

18. **Answer: D**

This young patient has an aortic root aneurysm measuring nearly 8 cm in diameter and aortic root replacement is indicated. Separately replacing the aortic valve and the tubular portion of the ascending aorta is not adequate because this would leave aneurysmal sinus tissue that would be prone to further dilation and eventual rupture or dissection. A mechanical composite valve graft will provide a durable root replacement in this patient. Tension-free reattachment of the coronary arteries is critical to prevent disruption of the coronary anastomoses and pseudoaneurysm formation. In most cases this can be accomplished by mobilizing the coronary arteries along with buttons of surrounding aortic tissue. In patients undergoing reoperations, especially those with extremely large aneurysms, it is often difficult to mobilize the coronary arteries enough to enable their direct reattachment to the graft without tension. In this situation the Cabrol technique may be the best option. Each coronary ostium is sutured to an end of a 10 mm graft, which is then connected to the aortic graft with a side-to-side anastomosis. Tension-free coronary reattachment is then achieved without extensive mobilization. Valve-sparing root replacement is an excellent option for young patients who need root replacement, provided that the annulus is not excessively dilated and the valve leaflets are in satisfactory condition. However, the severely dilated root, cusp prolapse, and fenestrated valve leaflets in the described patient make valve-sparing root replacement a less satisfactory option. Cryopreserved homografts are prone to degeneration, which becomes problematic in younger patients. Homografts are generally reserved for cases in which local infection makes it desirable to avoid using a synthetic graft and other prosthetic material.

19. **Answer: D**

All patients with Marfan syndrome require aggressive cardiovascular imaging surveillance including echocardiograms obtained at regular intervals. Patients with Marfan syndrome are at high risk of acute aortic dissection even when the aorta is only modestly dilated, and this is particularly true in patients with a family history of dissection. Therefore, aortic root replacement is recommended when the ascending aortic diameter exceeds 5.0 cm in patients with Marfan syndrome, in contrast to the 5.5-cm threshold generally used in non-Marfan patients. When patients with Marfan syndrome undergo isolated graft replacement of the tubular portion of the ascending aorta, progressive disease of the aortic root—including annuloaortic ectasia, aortic valve regurgitation, and acute dissection—invariably develops, necessitating complex reoperation. Therefore, ascending aortic repair should always involve full root replacement using either valve-replacing or valve-sparing techniques, even if the sinuses of Valsalva are not yet dilated and the aortic valve is competent.

Although treatment with β-blockers is currently standard for Marfan patients, the effectiveness of this therapy has not yet been proved. Recent experiments show that losartan, an angiotensin II type 1 receptor antagonist, prevents aortic dilatation in a mouse model of Marfan syndrome. This work has generated a current randomized clinical trial. Regardless of losartan's efficacy in preventing aneurysms, however, it will not replace surgical treatment for patients who have indications for aortic replacement.

20. **Answer: B**

Marfan syndrome is a heritable connective tissue disorder associated with severe orthopedic, ophthalmologic, and cardiovascular manifestations. The most common cardiovascular problem in patients with Marfan syndrome is aortic root aneurysm caused by progressive annuloaortic ectasia. If untreated, such aneurysms ultimately rupture, dissect, or cause severe aortic valve regurgitation. In addition to aortic root aneurysms, patients with Marfan syndrome are prone to mitral valve prolapse and to aneurysms and dissections involving the aortic arch and thoracoabdominal aorta. This propensity for developing multiple aortic aneurysms mandates that periodic aortic imaging be continued for life, even after a patient has undergone successful aortic root replacement. In most patients who meet the clinical diagnostic criteria for Marfan syndrome (i.e., the Ghent criteria), the disease is attributed to a mutation in the gene for fibrillin-1. Fibrillin-1 is a glycoprotein component of microfibrils, which are key structural components of the extracellular matrix within the media of the aortic wall. Elastin and collagen are the major components of the aortic wall matrix, conferring resilience and strength, respectively. Mutations that affect these proteins are responsible for other cardiovascular conditions. For example, the vascular form of Ehlers-Danlos syndrome is caused by mutations affecting type III collagen, and supravalvular aortic stenosis is caused by mutations affecting elastin. Mutations that affect a receptor for transforming growth factor-β have been described in patients with clinical features of Marfan syndrome, and these mutations have been recently shown to cause Loeys-Dietz syndrome, a condition associated with particularly severe aortic and peripheral vascular manifestations that require aggressive surgical treatment.

21. **Answer: A**

The patient has a strong family history of aortic dissection and enough stigmata to fulfill criteria for a diagnosis of the Marfan syndrome based on the Ghent nosology. The aortic root has a maximal orthogonal diameter of 50 mm. In combination, these findings should prompt aortic root replacement. Given his age, two appropriate options include a mechanical valve-conduit or valve-sparing aortic root replacement. Ascending aortic replacement is appropriate, but total aortic arch replacement is unnecessary and unjustified in this case given the normal caliber of the aortic arch. Replacement of only the noncoronary sinus using a modified remodeling technique is not an adequate procedure for an aortic root aneurysm in a Marfan patient. The tissue of the entire root is involved, even if the dilation is asymmetric. Similarly, a Wheat procedure (aortic valve replacement combined with supracoronary ascending aortic replacement) does not appropriately address the pathology of the aortic root. While losartan (angiotensin II receptor antagonist) administration may be beneficial to reduce the risk of progressive aortic dilation in Marfan children, this patient's aortic root has already dilated to a critical dimension. Expansion to 50 mm portends a significant risk of aortic catastrophe and justifies operative intervention at this time.

22. **Answer: D**

    The CT scan reveals an aneurysm that involves the ascending aorta, transverse aortic arch, descending thoracic aorta, and abdominal aorta. Patients with such large aneurysms involving both the proximal (ascending and arch) and distal (descending or thoracoabdominal) aortic segments present a clinical challenge. Replacement of both segments during a single-stage procedure is advocated by some surgeons, provided that the distal aspect of the aneurysm does not extend into the abdomen. When the distal aspect does involve the abdominal aorta, repair is generally performed in stages. The dilemma of which aneurysm to treat first is introduced. In general it is preferable to replace the proximal segment during the initial operation. This offers the advantage of allowing concomitant treatment of coronary artery and valvular disease. The elephant trunk technique can be used in these cases because it leaves a segment of graft suspended in the descending thoracic aorta, which simplifies the second operation. The distal segment is repaired first in patients in whom the thoracoabdominal aortic aneurysm is disproportionately larger that the ascending aortic aneurysm, or in whom the distal aneurysm is causing the predominant symptoms, as in the patient described here. When the distal segment is repaired during the first operation, the reversed elephant trunk technique–in which an 8 cm segment is invaginated into the upper end of the descending aortic graft—can be used to simplify reconstruction of the arch during the second operation.

23. **Answer: A**

    When a patient presents with aneurysms involving the ascending and thoracoabdominal aortic segments, the decision about which aneurysm to treat first is based on three major factors. The presence of symptoms is the most important consideration, and the lesion causing the most life-threatening symptoms should be repaired first. Second, the presence of correctable cardiac disease is an issue because clamping the descending thoracic aorta induces substantial cardiac stress. Addressing correctable coronary and valvular disease first reduces the risk of cardiac complications during the thoracoabdominal aortic repair. A third consideration relates to assessing the relative sizes of the aneurysms. When one aneurysm is disproportionately larger than the other, the larger aneurysm is treated first. Because this patient has symptoms of aortic valve regurgitation and no symptoms related to the thoracoabdominal aortic aneurysm, the most appropriate choice is to address the aortic valve, ascending aorta, and transverse aortic arch first. Using the elephant trunk technique, which leaves a segment of graft suspended in the descending thoracic aorta, simplifies the second operation. This patient's aortic root is not enlarged, so root replacement is not warranted.

24. **Answer: D**

    Myocardial protection during prolonged cooling for circulatory arrest can be challenging in patients with ascending/arch aneurysms and aortic valve regurgitation. The incompetent valve allows pump flow to distend the fibrillating left ventricle and causes a marked increase in sump drainage. If not corrected, ventricular distention will cause increased myocardial oxygen demand and decreased subendocardial perfusion. The resulting inadequate myocardial preservation will lead to severely impaired postoperative cardiac function. Adding another ventricular sump may lessen distention but will not correct or reliably control this problem. The best way to protect the myocardium is to induce cardioplegic arrest as rapidly as possible after fibrillation. When anatomically feasible, the aneurysmal ascending aorta should be clamped. This will stop the inflow into the distended left ventricle, increase systemic flow, and allow delivery of cardioplegia. In the described patient, the ascending aorta is not dissected and atheromata are not prominent so it can be clamped safely. Placing a needle in the ascending aorta is unlikely to allow adequate cardioplegia delivery, as the cardioplegia will flow through the regurgitant valve instead of pressurizing the root and perfusing the coronary arteries. The best approach is to open the ascending aorta and deliver cardioplegia directly into the coronary ostia. When clamping the aorta is not possible (e.g., in patients with enormous aneurysms, see figure) delivering continuous retrograde cardioplegia while manually decompressing the ventricle and continuing rapid cooling may be the only option.

25. **Answer: D**

    This apparently healthy man has a dilated ascending aorta with a maximum orthogonal diameter of 44 mm that was incidentally identified during evaluation for an upper respiratory infection. He has no family history of an aortic aneurysm or aortic catastrophe, no stigmata of a connective tissue disorder and he is not hypertensive. Consequently, there is no justification for aortic replacement at this time as the risks of operation exceed the risk of a catastrophe of a 44 mm aorta in a tall 62-year-old man. In asymptomatic patients risk factors that prompt operation include rapid growth (e.g. >5 mm/year) or an aortic index (see below) greater than 1.5. This corresponds roughly to a diameter of 50–55 mm for a man this size.

    Oral losartan is currently under investigation for use to prevent aortic root dilatation in patients, particularly children, with Marfan syndrome. However, for a patient with a dilated ascending aorta but neither hypertension nor Marfan syndrome, there is inadequate evidence to justify its use. This patient requires long-term surveillance of his ascending aorta from this point forward. Annual cross-sectional imaging is appropriate since he has no clinically significant aortic valve regurgitation. Considering improved safety of large-scale vascular operations and the evolving alternative to open procedures, there are parallel relaxations of the data-driven "hinge points" at which relative risks are balanced. In Marfan and collagenopathy patients one suggested trigger for intensive surveillance (if not intervention) is an absolute diameter of 40 mm or a calculated "aortic index" greater than 1.3. A value ≥1.5 is considered a clear operative threshold for these at-risk patients by some experts. For patients without connective tissue concerns, these threshold values are somewhat higher. The aortic index calculation (maximum measured orthogonal diameter/predicted diameter for the age, sex and body surface area) was described by Roman et al. in 1989. The formulas, derived from echo measurements of normal patients, for predicted sinus dimensions are:

- Children (<18 years): 1.02 + (0.98 × BSA (m^2))
- Adults (18–40 years): 0.97 + (1.12 × BSA (m^2))
- Adults (>40 years): 1.92 + (0.74 × BSA (m^2))
- Regarding the described patient (BSA calculates to 2.13 m^2):
- aortic index = 4.4/(1.92 + [0.74 × 2.13])
  = 4.4/(1.92 + 1.58)
  = 4.4/(3.5)
  = 1.26, which rounds up to 1.3, so the threshold for surveillance (but not for operation) has been reached.

26. **Answer: D**

Intraoperative epi-aortic ultrasound is a sensitive method to identify and determine the severity of aortic atherosclerosis. There are several systems for grading the severity of aortic atherosclerotic disease, but all of them consider atheroma thickness greater than 5 mm to be severe. Increasing severity of aortic atheromatous plaque is associated with an increasing risk of neurologic complications. Minimizing aortic manipulation by using alternate cannulation sites and avoiding aortic clamping is the cornerstone of reducing the risk of neurologic complications in patients with aortic atheromata. This is a particular challenge for those who require aortic valve replacement because perfusion and myocardial protection options must be identified. Because this woman's ascending aortic atheromata extend into the arch, the ascending aorta should not be cannulated or clamped. The aortic clamp can be eliminated by replacing the aortic valve during a period of deep hypothermic circulatory arrest. The femoral artery is not an ideal cannulation site in this case because of the risk of retrograde embolization of atheromatous debris from the abdominal and descending thoracic aortic segments. The axillary artery is usually free of atherosclerotic disease and, therefore, represents an excellent alternate cannulation site in this situation.

27. **Answer: C**

This patient's residual type B aortic dissection has become aneurysmal. The maximal orthogonal diameter at the distal arch and proximal descending thoracic aorta exceeds 65 mm. Additionally, his hypertension is refractory to a five-drug antihypertensive regimen, and he is symptomatic with upper thoracic back pain. He is already on both a beta-blocker (metoprolol) and an α-blocker (doxazosin), so adding labetalol would likely offer little benefit. Continued medical management is not appropriate. Stent-grafting a chronic, dissected thoracoabdominal aortic aneurysm, particularly in a young, otherwise healthy patient, is appropriate only on an experimental basis at this time.

This patient's aorta is dilated down to the celiac artery, but the infrarenal aorta is of normal caliber. Replacing the entire thoracoabdominal aorta is unnecessary given the extent of dilatation. It would pose added risk of paraplegia, especially in the setting of dissection. Descending aortic replacement alone would leave residual dilated aorta near the diaphragm, and using a clamp-and-sew technique would add significant risk of paraplegia in this setting. Extent I thoracoabdominal aortic replacement using left heart bypass is suitable for this patient. The patient has bovine arch anatomy and it is likely that a safe clamp site could be established between the left subclavian and the innominate trunk. Using deep hypothermia for spinal cord protection is also appropriate, although it adds time to the operation time and may increase blood transfusion requirements.

28. **Answer: C**

A critical aspect of surgical decision making about aortic disease is appreciating the point at which the potential benefits of an operation, in terms of preventing rupture or acute dissection, outweighs the risks the operation entails. Outcomes after elective repair of ascending aortic aneurysms are excellent, as several series report mortality rates less than 5%. Recent natural history studies show that patients with ascending aortic aneurysms are at low risk of catastrophic events until the aortic diameter exceeds 6.0 cm (see figure). This finding supports elective repair of ascending aortic aneurysms that reach a diameter of 5.5 cm, before they reach the critical size threshold. Lower absolute diameter triggers are applied to patients with heritable connective tissue disorders, including Marfan syndrome and Loeys-Dietz syndrome, or a family history of aortic dissection. Other recommended indications for repair include symptomatic aneurysms (regardless of diameter) and those observed to increase in diameter 1.0 cm or more within a year.

29. **Answer: A**

    The CT angiogram shown reveals a Type B intramural hematoma (IMH) with a penetrating atherosclerotic ulcer (PAU). As the name implies, PAU is associated with severe atherosclerotic disease and the radiologic appearance is similar to ulceration in the GI tract. The natural history and best treatment of PAU is somewhat controversial. Recent studies suggest that conservative treatment is appropriate under most conditions. However, close clinical follow-up is mandatory as thin-walled saccular pseudoaneurysms or rupture may occur. This patient's ipsilateral pleural effusion heightens concern for such complications, and TEE may define the local anatomy more precisely. While endoaortic stent grafting might appear to be well suited for a localized PAU, severe atherosclerosis in the aorta and the embolic risk of manipulation, the risk of paraplegia and access difficulties moderate these considerations. The current clinical experience with endografting for IMH-PAU is meager. Intramural hematoma was initially thought to result from rupture of *vasa vasora*, though there is little evidence to support this theory. Others believe that IMH is always associated with some degree of intimal tear that may go undetected. The case of PAU with IMH, as is in this patient, appears to contradict that theory. On CT or MRI imaging IMH appears as a crescentic or concentric wall thickening greater than 0.5–0.7 cm. This represents medial degeneration with hematoma within the media, though at a location closer to the adventitia compared to the pathology of aortic dissection. The natural history of IMH is more benign than aortic dissection, perhaps due to a lower associated incidence of malperfusion syndromes. Aortic dissection, rupture or late progression to aneurysm may evolve from IMH. Like aortic dissection, IMH is categorized as type A (involving the ascending aorta) or type B (isolated to the descending aorta). Type B, as in this case, has a less malignant course. Complete resolution of the hematoma has been observed in 50–80% of cases with conservative management. Predictors of progression include the presence of PAU, older age, aortic diameter greater than 4.0–4.5 cm, and hematoma thickness greater than 1 cm. Nonoperative management of type B IMH is widely accepted. Controversy exists regarding the management of type A IMH, with some advocating intervention only in cases of complication (dissection, expansion, rupture) while others propose a more aggressive approach. If conservative management is chosen, patients require inpatient observation in the ICU with bed rest for 2 weeks and vigilant blood pressure control. Repeat imaging by CT or MRI is mandatory every few days, as is repeat echocardiography.

30. **Answer: C**

    Intracranial hemorrhage is an uncommon but potentially catastrophic complication of cerebrospinal fluid drainage. Because this complication may require emergent neurosurgical intervention, all patients who have had cerebrospinal fluid drainage (CSF) should undergo immediate computed tomography of the head if postoperative headache develops. The most likely cause of the headache is a CSF leak. There is usually no external wetness, because the fluid generally leaks into the tissue surrounding the dural opening rather than through the puncture site in the skin. Headaches caused by CSF leaks are typically positional, i.e., symptoms are much worse when the patient sits or stands. They are often accompanied by sensitivity to light. Most headaches caused by cerebrospinal fluid leaks require treatment with an epidural blood patch, but this should only be considered after intracranial bleeding has been ruled out. In many cases, the patient is unable to get out of bed before definitive treatment. Early treatment, therefore, expedites overall postoperative convalescence because it enables the patient to resume ambulation.

    It is unlikely that this patient has meningitis, an extremely rare complication of lumbar drain insertion, given the absence of fever and leukocytosis. Furthermore, collecting CSF is contraindicated until imaging has excluded the presence of an intracranial process. Similarly, reinserting a cerebrospinal fluid drain is contraindicated, because this would probably worsen the symptoms.

31. **Answer: E**

    This man has developed acute, delayed paraplegia following thoracoabdominal aortic replacement that is likely secondary to hypotension caused or exacerbated by starting a propofol infusion for sedation. Delayed paraplegia is a well-known phenomenon that occurs after thoracoabdominal aortic surgery and is often due to hypotension in a watershed zone of devascularized spinal cord. If treated immediately it can often be reversed by improving spinal perfusion pressure. This is best achieved by a combination of hypertensive treatment and lumbar CSF drainage. Vasopressors (e.g. norepinephrine, neosynephrine, or vasopressin) can be used to initiate hypertension. Mean arterial pressure (MAP) should be increased stepwise every few minutes until an improvement in the lower extremity neurologic exam is noted (initial MAP target pressure is above 90 mmHg). Several factors are involved with most cases of delayed onset paraplegia, and its prognosis is much better than paraplegia noted immediately at the end of aneurysm repair. In this case, the spinal (or cerebral) perfusion pressure was only 41 mmHg (MAP-CVP) when neurologic changes were noted. The propofol infusion should be discontinued immediately and a vasopressor infused to reverse the hypotension. There is already a lumbar CSF drain in place because the intrathecal pressure is provided, but a new drain is indicated if there is a question about its function. The drain should be opened to drop intrathecal pressure to below 10 mmHg to further improve spinal perfusion pressure. MR angiography might help define a region of infarction, but it is an inappropriate first step in management because treatment would be delayed. Nicardipine is an antihypertensive drug, which is contraindicated in this setting. Naloxone (Narcan) has been used in the setting of acute paraplegia following thoracoabdominal aortic replacement, but its efficacy is not well-established. Its use as an adjunct would be secondary to the primary therapies (hypertensive therapy and CSF drainage).

32. **Answer: C**

    Lower extremity paralysis or weakness due to spinal cord ischemia remains a major complication of thoracoabdominal aortic aneurysm repair, particularly after Crawford extent II repairs. Nearly two-thirds of patients in whom paraplegia or paraparesis develops have the deficit immediately upon awakening from anesthesia. The other third of patients are neurologically intact initially, but the deficit develops at a median of 3 days after operation. Once the deficit occurs, cerebrospinal fluid drainage should be initiated as soon as possible, because lowering intrathecal pressure has been associated with rapid recovery of motor function. Hypotensive episodes are associated with about one-fourth of cases of delayed paraplegia. Causes of hypotension (arrhythmia, sepsis, hypovolemia, pneumothorax, antihypertensive medications, etc.) must be identified and treated aggressively, and vasoactive medications should be administered to raise the mean arterial blood pressure to 90–100 mmHg. It is also prudent to correct anemia in order to optimize oxygen delivery. The described patient has an adequate blood pressure (estimated MAP = 101 mmHg) and only mild anemia. Therefore, insertion of a cerebrospinal fluid drain should be the first intervention in this case. Although thrombosis of intercostal arteries has been proposed as a potential inciting event in some patients, imaging may be difficult and reoperation to re-establish spinal cord perfusion is seldom feasible. There is no evidence that anticoagulation has therapeutic benefit in this situation and it could increase the risks associated with inserting a lumbar drain.

33. **Answer: B**

    Based on the symptoms of exercise-induced syncope and pre-syncope with a history of previously covered left subclavian artery (see CT angiogram), vertebrobasilar insufficiency due to left subclavian steal is suspected. The patient has excellent collateral blood flow to the left arm as evidenced by the minimal blood pressure gradient across both arms at rest. With a greater metabolic demand during upper extremity exercise the blood flow in the left vertebral artery may reverse, a possibility best documented by cerebral angiogram or time-of-flight magnetic resonance angiography. Cerebral angiography facilitates better left upper extremity provocative testing than MRA, but either can be helpful in the diagnosis. Carotid studies should also be done, but it is not expected that abnormal findings will explain this patient's symptoms.

    Once reversal of vertebral arterial blood flow is demonstrated, either carotid-to-subclavian bypass or transposition is appropriate therapy. Direct left vertebral arterial bypass, although possible, does not specifically address the phenomenon of steal to the left arm, and it is more cumbersome than simple revascularization of the left subclavian artery. The phenomenon of left subclavian steal is now a recognized complication of left subclavian arterial coverage by thoracic aortic stent grafts.

34. **Answer: A**

    Patients with high-speed deceleration injuries are at risk for aortic transection at the level of the ligamentum arteriosum just beyond the left subclavian artery. The diagnosis is often made on CT scan but may require aortography or transesophageal echo evaluation to confirm the injury. Regardless of how the diagnosis is made, intra-abdominal and intracranial injuries should be addressed first. Patients with concomitant injuries to the thoracic aorta and abdomen should have exploratory laparotomy prior to repair of the aortic injury. The aortic injury is usually addressed by open repair through a left thoracotomy. Similarly, patients with an epidural hematoma should have a craniotomy prior to aortic repair. Stent-graft repair of traumatic aortic transection may also be an option and may become the treatment of choice in the future. Despite the less invasive nature of stent grafting, however, it is not applicable to all transections and it still requires anticoagulation and considerable time. It should not supercede laparotomy or craniotomy. Some scenarios involve delayed identification of aortic transection and a nonoperative approach may be appropriate include: coexisting severe COPD or cardiac disease; a patient with severe head injuries whose prognosis for neurologic recovery is uncertain; patients with sepsis following intra-abdominal injuries (e.g., colon perforation) to minimize the risk of graft infection; patients with concomitant burns and those with severe right lung contusions who may not be able to tolerate single lung ventilation. Aggressive beta blockade and invasive monitoring for blood pressure control is mandatory in all patients with this injury. Serial imaging of the aortic injury may also be helpful in determining the appropriate time to intervene surgically.

35. **Answer: B**

    This man has sustained a traumatic aortic transection near the isthmus of the aorta, and there is a distal aortic dissection. The extent of the aortic abnormalities are not clear from the limited CT slices. Additional injuries include chest wall trauma, a femur fracture and a cerebral contusion. Although he is hemodynamically stable at the time of evaluation his greatest risk for in-hospital death remains exsanguination from aortic rupture into the left pleural space. In the setting of concomitant neurologic injury, optimal contemporary management is endovascular stent-grafting. The proximal descending thoracic aorta is quite conducive to endovascular repair. The caliber of this patient's aorta appears large enough to accept a thoracic aortic stent graft. Open reconstruction with hypothermic circulatory arrest should be avoided in the setting of concomitant brain injury especially when there is intracranial hemorrhage. Craniectomy is not indicated without signs cerebral edema or bleeding. Open reconstruction utilizing left heart bypass is an acceptable treatment option, and it would be optimal treatment for a small-caliber (<17 mm) aorta. However, in the setting of multiple other injuries endovascular stent-grafting offers more timely therapy at a lower operative risk to this patient.

36. **Answer: C**

    The described situation is likely due to dynamic obstruction of one or more of the brachiocephalic arteries by the dissection flap. Either cannulation of the false lumen in the groin or a re-entry tear between the femoral artery and the aortic arch can cause excessive pressure in the false lumen near the arch. The result can be obstruction of blood flow into the true lumen of the arch branch vessels. Devastating neurologic injury from inadequate flow will follow if hypoperfusion is not immediately addressed. Applying a cross-clamp could worsen this situation and would certainly not improve it. Rewarming the patient reverses an important aspect of cerebral protection and further delays definitive therapy for the proximal aortic dissection. Recannulation through the left femoral artery may reconstitute true lumen flow if the problem was due to false lumen cannulations. It will not address obstructive flap dynamics associated with retrograde perfusion. Cannulation of the right subclavian artery is most likely to restore cerebral perfusion under the described circumstances. Central aortic cannulation of the true lumen, if possible, would accomplish the same goal, but identification of undissected ascending aorta is seldom possible. Attempting to expedite reaching deep hypothermia using excessive cooling gradients can potentiate cerebral vasoconstriction and non-uniform cooling of the brain, which may actually worsen prospects for cerebral protection. Without assured cerebral flow, this strategy is folly.

37. **Answer: C**

    This patient presented with an acute Stanford type A aortic dissection with intramural hematoma. She is hypotensive and intrapericardial blood clot is obvious on the CT study, which indicates probable rupture. She should be taken emergently to the operating room for definitive repair. Stent-grafting the ascending aorta is inappropriate therapy for an acute type A dissection. Replacement of the entire aortic root is probably not required in this patient because gross dilation of the root is not obvious, and the study suggests that only a small portion of the non-coronary sinus is dissected. If, indeed, the other two sinuses are spared, then the goal should be to preserve the native valve. Root repair with valve resuspension in this age group is easier and carries an acceptably low risk of late failure. Aortic root replacement with a mechanical valve conduit would address the problem definitively, but this offers no advantage over bioprosthetic root replacement for a patient of this age. A mechanical valve conduit requires long-term anticoagulation, and the 15- to 20-year survival after type A dissection repair in this age group does not justify the added challenges of warfarin management. Complete reconstruction of the entire involved aorta is seldom possible since most ascending dissections propagate and have fenestrations distally in the descending aorta. This patient's CT study shows no descending dissection, so resection of the entire ascending aorta and involved arch is feasible. Total aortic arch replacement is not necessary in most acute type A dissections, and this therapy alone does not address the primary goals of type A dissection repair: restoration of aortic valve competency, resection of the primary tear site, restoration of true lumen blood flow, and exclusion of the false lumen.

38. **Answer: C**

    Normal atrioventricular (A-V) conduction directs the electrical impulse from the SA node though the AV node to the His bundle and down the Purkinje cells. The A-V node creates an electrical delay prior to the impulse entering the His bundle. The central fibrous body normally acts as a functional electrical insulator from abnormal A-V conduction. If there is an accessory A-V conduction connection (Kent bundle), then more rapid antegrade conduction down this pathway may occur. This pre-excitation translates to a short P-R interval and a delta wave noted on the ECG. These features are apparent in the augmented figure. This patient has Wolff-Parkinson-White (WPW) syndrome. Reciprocating tachycardia can develop if an accessory pathway functions as part of a re-entrant conduction loop. Either the Kent bundle or the normal A-V node can conduct these impulses, but each can function in one direction only. If A-V conduction is normal and the impulse returns via the accessory bundle it is termed orthodromic. If antegrade conduction is via the accessory pathway and reentry is backward through the A-V node, it is antidromic. Rapid tachycardia can occur in either case, with the upper rate limited only by the refractory periods of the pathways. The ventricular response may be fast enough to be inefficient and cause low cardiac output symptoms or sudden death. Development of atrial fibrillation can certainly be dangerous.

WPW and other accessory pathway-mediated tachycardias were once surgical diseases, but now they are best treated by percutaneous mapping and ablation of the accessory pathway. A MAZE procedure or unmapped left atrial ablation will not offer the requisite precise identification or destruction of this patient's accessory pathway. Since the A-V node is not the abnormality, node ablation and permanent pacing is not appropriate. Most patients with WPW syndrome have few symptoms and chronic drug therapy is undesirable and not reliably effective. A primary challenge is to determine when ablation is warranted.

39. **Answer: D**

In most cardiac transplant centers immunosuppression after heart transplantation consists of a calcineurin inhibitor (tacrolimus or cyclosporin) and an adjunct immunosuppressant with or without maintenance corticosteroids. The nephrotoxicity of calcineurin inhibitors is well established and in the face of declining renal function this class of drugs should be discontinued and the renal function followed closely.

Other immunosuppressants can be maintained. Supportive care should concentrate on maximizing cardiac output at modest preload. Atrial pacing and/or isuproterenol infusion should achieve a heart rate of 110, and diuretics should be used to maintain brisk urine output. Left and right heart afterload can be independently managed to maintain systemic perfusion yet minimize pulmonary pressures. This patient's tacrolimus can be restarted when creatinine is returning to baseline.

40. **Answer: C**

Standard maintenance triple therapy following cardiac transplantation includes one drug from each of the following classes:

1. Calcineurin inhibitors: cyclosporine, tacrolimus
2. Corticosteroids: prednisone, prednisolone
3. Antimetabolites: azathioprine, mycophenolate mofetil

The use of rapamycin (Sirolimus) is being introduced into cardiac transplantation. It is used more routinely in abdominal organ transplantation. It targets preventing the actions of a key kinase called target of rapamycin (TOR). There are concerns that wound healing complications may increase when rapamycin is given early after sternotomy.

Antibody therapy with monoclonal (OKT3) or polyclonal (antilymphocyte globulin, ALG or antithymocyte globulin, ATG) agents is used as induction therapy or salvage therapy for acute rejection episodes, but not for maintenance immunosuppression.

41. **Answer: C**

This patient now has strong evidence for endocarditis, and the constellation of symptoms and findings on admission was consistent with a diagnosis of bacterial endocarditis (positive for two to three major criteria and at least two minor criteria of the Duke Endocarditis Service). The involvement of the surgeons was late in this patient's course and his prognosis has worsened with renal failure and ongoing congestive heart failure. The chest film shows pulmonary edema with a normal heart size, which strongly suggests acute, severe aortic regurgitation. No matter what complications have developed or how much decompensation has progressed, aortic valve endocarditis with severe regurgitation and heart failure must be repaired or mortality is assured. The source(s) of infection must be identified and eradicated, and hemodynamics must be corrected by replacing the valve. Emergency aortic valve replacement (with root debridement) is appropriate in this setting, but operation should be preceded by a CT scan of the brain and abdomen. Twenty-four to sixty-seven percent of patients with endocarditis have systemic embolization, over half of which involve the brain. An active infarct or abscess requires reconsideration of treatment strategies and timing. Five to nineteen percent of emboli occur to spleen, and either preliminary or concomitant splenectomy is prudent if a splenic abscess is found. Echocardiography is critical to the diagnosis of endocarditis, and the size of vegetations, local extension, and severity of aortic valve regurgitation are factors that influence the likelihood of medical therapy success for native valve infection. Renal failure in patients who have endocarditis is often related to immunologic phenomena (glomerulonephritis) with contribution from emboli, sepsis, and hemodynamic abnormalities.

42. **Answer: C**

ACC/AHA guidelines are classified both by the strength of recommendation and the quality of evidence supporting the recommendation. Class I recommendations are those for which "there is evidence for or general agreement that the treatment is beneficial, useful, and effective." Class II recommendations are those for which there is conflicting evidence or a divergence of opinion about the efficacy of a treatment. If the weight of opinion is in favor of the treatment these recommendations are graded Class IIa. Class IIb recommendations are those for which treatment efficacy is less well established. The internet link supplied outlines current guidelines for care of patients with valvular heart disease. The timing of surgery is a key part of optimizing surgical management of endocarditis. Patients should be taken to the operating room regardless of the duration of antimicrobial therapy when there is an indication for surgery. Current ACC/AHA class I indications for surgery in native valve endocarditis include:

1. any acute valve lesion resulting in heart failure
2. aortic or mitral regurgitation with hemodynamic evidence of elevated left ventricular end-diastolic or left atrial pressures or moderate pulmonary hypertension
3. structural complications such as annular or aortic abscess, or other destructive penetrating lesions including fistulae and "kissing lesions"
4. fungal or other highly resistant organisms

Native valve endocarditis complicated by recurrent emboli and persistent vegetations despite appropriate antibiotic therapy is a class IIa indication for surgery, and the presence of mobile vegetations in excess of 10 mm with or without emboli is classed by the ACC/AHA guidelines as a class IIb indication for surgery. In this patient, heart failure with pulmonary edema is an urgent indication for surgery. Other indications exist, but they do not justify emergent operation: anterior leaflet perforation will eventually need surgery; a mobile vegetation without embolization is likely to be watched in an elderly patient; *Streptococcus bovis* is a sensitive organism which can often be eradicated by antibiotic therapy; and an elevated WBC at this point in his treatment does not constitute uncontrolled sepsis.

43. **Answer: A**

Although we have the technology to perform complex operations, one must weigh the expected outcome against the risk. Elderly patients (over age 75) may be able to tolerate a major operation under ideal conditions, but the addition of major comorbidities makes the chance of success far less likely. Many patients and their families anticipate only successful outcomes and do not understand the significance of survival with major complications. The patient presented here has an overwhelming chance for death regardless of the therapeutic intervention.

Breaking bad news to families is not easy for a surgeon. Many hospitals have resources including Ethics Committees available to help in such situations. Nine general points for consideration are suggested:

1. prepare for discussion by ensuring all information/facts/data are available
2. deliver an analysis in person in a private area without interruptions
3. establish patient and/or family knowledge and understanding of the illness
4. establish what/how much the patient and/or family want to know
5. deliver information in a sensitive, straightforward manner, avoiding technical language and euphemisms
6. check for understanding and clarify concepts and terms
7. respond by using active listening, encouraging expression of emotions
8. organize an immediate therapeutic plan that addresses the patient's and family's concerns and agenda
9. reassess understanding of the condition and treatment plan and determine the need for further education and follow-up

44. **Answer: E**

Criteria for catheter intervention for mitral stenosis are based on symptoms, valve characteristics and pulmonary artery pressures. A symptomatic patient (NYHA class II or worse) must have favorable valve morphology and moderate or severe mitral stenosis and/or PA systolic pressure >50 mmHg at rest (or >60 mmHg with exercise to satisfy ACC/AHA Class I indications for percutaneous mitral balloon valvotomy/valvuloplasty. Favorable valve morphology includes non-calcified, pliable mitral valve leaflets. Mitral valve morphology is most important determinant of immediate post-valvotomy hemodynamic results and long-term clinical outcomes. Patients with valvular calcification, thickened and fibrotic leaflets with decreased mobility, and subvalvular fusion have a higher incidence of acute complications and a higher rate of recurrent stenosis on follow-up. Therefore, marked fusion of the leaflets and subvalvular apparatus and severe commissural calcification are relative contraindication to percutaneous balloon mitral valvotomy. The Wilkins scoring system grades mitral valve morphology using four echocardiographic characteristics: leaflet mobility, leaflet thickening, valve calcification and involvement of the subvalvular apparatus. Each parameter is graded from 0 to 4. A total score of more than 8 predicts a low success with percutaneous mitral valvuloplasty. Other relative contraindications to this procedure include left atrial thrombus and mitral regurgitation that is worse than mild. The thresholds for mitral valve surgery for stenosis have historically been more conservative than for regurgitation. The potential for durable repair is much lower, and MVR is generally reserved for symptomatic patients or those with severe pulmonary hypertension. The described patient has NYHA class II symptoms and moderate mitral stenosis. Scoring contraindicates percutaneous balloon mitral valvotomy, and conventional recommendation is medical management with follow-up in 6 months.

45. **Answer: A**

Mitral regurgitation secondary to myocardial infarction is usually secondary to ventricular dysfunction and regional wall motion abnormalities. Occasionally the cause is rupture of a papillary muscle. In general, patients who require urgent or emergent operation for mitral regurgitation in the setting of acute myocardial infarction are at high risk for death and morbidity. The risks might be lower with papillary muscle rupture because mechanical dysfunction of the valve contributes to the regurgitation in addition to the mechanical dysfunction of the ventricle. However, this is not a proven assertion.

Concurrent revascularization lowers perioperative mortality and all critical abnormalities should be addressed at the time of operation. Residual mitral regurgitation after repair generally will not improve with expectancy or with mechanical support. In the case of complete papillary muscle rupture, many surgeons recommend immediate chordal sparing valve replacement. The size of the left ventricle, patient age, ventricular function, preoperative atrial fibrillation, and the preferences of surgeon and patient should all be considered when determining the type of prosthesis used.

46. **Answer: A**

Tools available to treat mitral systolic anterior motion include discontinuation of inotropic agents, additional volume, added alpha agents and, possibly, β-blockade. When these maneuvers fail to reverse SAM the cause is usually a discrepancy between the residual anterior and posterior leaflet heights and the septal-lateral diameter of the mitral annulus following ring annuloplasty. The type of ring annuloplasty does not influence the risk of SAM, and this condition has been reported with essentially all types of annuloplasty rings (flexible, rigid, semi-rigid rings and partial or complete designs). This complication can occur in the absence of an annuloplasty ring, so changing the ring to an incomplete band is unlikely to resolve SAM. Sizing the ring is a more critical issue, but since a 40 mm ring is the largest commercially available size, a larger ring is not an option in the described case. Removing the ring could resolve the SAM, but absence of a ring in degenerative repair can predispose to recurrent mitral regurgitation in the long term. The likely cause of SAM in this case is excess residual posterior leaflet tissue. Although the posterior leaflet is tall, the repair was undertaken with minimal resection techniques (triangular resection and artificial chordae). The residual posterior leaflet height is likely displacing the anterior leaflet into the left ventricular outflow tract. A sliding posterior leaflet plasty would have been appropriate during the initial operation to minimize the risk of SAM. At this point, however, it would be necessary to remove the ring and a longer period of cross clamping and bypass would be required. Mitral valve replacement is usually not necessary and it should be avoided in this young woman. Repair is better because valve replacement would shorten her life expectancy, increase the lifetime risk of stroke and potentially complicate childbirth. One effective solution is to shorten the anterior leaflet. This is achieved by making a transverse incision toward the base of the anterior leaflet and re-suturing (which will shorten the leaflet by 5–7 mm) or to resect a 2–3 mm transverse ellipse of the leaflet before re-suturing (which will shorten the leaflet by 7–10 mm). A triangular resection of A2 is another option to shorten its length. Another option is to use a shorter PTFE chord to lower the margin of the posterior leaflet further down into the ventricle, moving the closure line more posteriorly and aligning the anterior leaflet away from the outflow tract. Finally, a recently proposed technique of posterior leaflet shortening by pledgeted sutures through the leaflet and under the annuloplasty ring has promise as an equivalent to sliding plasty.

47. **Answer: C**

Mitral valve repair offers superior long-term survival, freedom from cardiac morbidity, and better quality of life in most patients with severe mitral regurgitation compared to medical management and mitral valve replacement. It is the treatment of choice in these patients because it is the only treatment that restores normal life expectancy to otherwise healthy patients with advanced degenerative mitral valve disease.

Factors determining timing of surgery for isolated mitral regurgitation in the current ACC/AHA guidelines include symptoms, left ventricular ejection fraction (≤60%), left ventricular end-systolic dimension (≥40 mm), atrial fibrillation, and pulmonary hypertension (PA systolic >50 mmHg at rest or >60 with exercise). While there is a consensus that patients in whom mitral repair is feasible should undergo surgery before left ventricular decompensation is documented, the poorer outcomes associated with mitral replacement mean that asymptomatic patients with severe mitral regurgitation but preserved left ventricular function should not undergo surgery unless a greater than 90% successful repair rate is likely. Mechanical replacement should not be contemplated for the described patient. Successful repair and maintenance of normal sinus rhythm will obviate the need for warfarin, so the acceptability of this drug is not a relevant factor in the timing of surgery. Patients of all ages, including the elderly, are likely to benefit from mitral valve repair, and age is not an important consideration in the utility of surgery in this patient. The key issue, therefore, in deciding to operate on this patient is the likelihood of achieving a durable repair. The patient has Barlow's disease. Echocardiogram in this condition shows a mitral valve with markedly excess tissue involving multiple leaflet segments in an otherwise large valve. Leaflet tissue is thickened and redundant with elongated chordae. Regurgitation is due to bi-leaflet, multisegment prolapse. Obtaining a competent and durable repair is more challenging in Barlow's disease, where tissue resection, sometimes of multiple leaflet segments, and chordal reconstruction are mainstays of repair. Although several isolated series report repair rates for degenerative disease of 90%, repair rates in developed countries continue to average between 50% and 70%. Echocardiographic assessment is key in matching surgical expertise to valve complexity. The probability of successful repair of an isolated P2 prolapse secondary to chordal rupture due to fibroelastic deficiency is high in most centers. However, even an experienced mitral repair surgeon may lack sufficient experience with Barlow's disease to offer this patient with complex bi-leaflet prolapse a >90% probability of repair. Analysis of valve repairability based on the specific echocardiographic lesions identified is the single most important factor in deciding whether to proceed with early surgery an asymptomatic patient.

48. **Answer: E**

The right mini-thoracotomy approach is a versatile incision for exposure to the mitral valve. Success is predicated upon free access through the anterior right hemithorax and a lateral approach to the inter-atrial groove. Pre-existing obliteration of the pleural space due to adhesions from prior right chest surgery or pleurodesis is a relative contraindication. While peripheral vascular disease is a contraindication to retrograde arterial perfusion, both ascending aorta and axillary artery are possible perfusion inflow sites with the right anterior mini-thoracotomy approach. Pectus excavatum, with the attendant leftward shift of the heart can make reaching the mitral valve exceedingly difficult if not impossible. *Pectus carinatum* ("pigeon breast") is not a problem. Previous CABG can make a right-side approach preferable to repeat sternotomy due to the avoidance of patent grafts and other adherent mediastinal structures. Concomitant tricuspid valve procedures are easily performed through this approach.

49. **Answer: A**

Decisions regarding the management of significant posterior bleeding and/or hematoma after a cardiac operation can be difficult. Inappropriate or incorrect decisions can have catastrophic consequences. A hematoma or arterial bleeding from the back of the heart after mitral valve surgery can represent a highly lethal atrioventricular dissociation. Patients at risk for this typically have severe mitral annular calcification that may require aggressive debridement prior to mitral valve replacement. As a general rule, the heart should not be lifted after mitral valve operations. Minor posterior bleeding should be managed expectantly. If there is significant arterial bleeding, however, then repair is mandatory. The problem must be identified and it is likely that a complex repair is required. Bypass must be resumed immediately. For internal repair, following cardioplegia the valve must be inspected, the ring or prosthesis should be removed and a generous pericardial patch repair may be required to obliterate the annular defect from within the heart. Various external patch and glue techniques have been reported for isolated cases. Fortunately, this complication follows only 1–2% of MVR procedures and it is rare following mitral valve repair. Individual surgeon or institutional experiences are small. As may be expected when numerous methods of repair are described, results are generally poor. Attempts at external direct repair on a loaded, beating heart almost always fail. With a prosthesis in place the exposure necessary to place pledgeted sutures will further disrupt the annulus, worsen bleeding, waste time and make successful definitive repair even more difficult. The isolated hematoma with modest bleeding described suggests a less catastrophic complication, but coronary sinus injuries associated with retrograde cardioplegia techniques can also be difficult to manage. Risks for coronary sinus injuries include hypertrophied hearts in elderly patients with friable tissue. If encountered at the start of the operation, the cannula should be removed and an alternative myocardial protection plan implemented. Repair can be with an onlay patch or by direct suture repair. Direct repair can result in a coronary sinus stricture, which may result in thrombosis and a potentially lethal outcome. Following a mitral intervention these injuries do not lend themselves to isolation or bypass grafting. If the hematoma is stable following protamine administration, then further manipulation of the area should be avoided since the low pressure venous system will typically stabilize and heal without intervention. Exploring a stable hematoma in such a situation can result in uncontrolled bleeding and potentially fatal ventricular injuries.

50. **Answer: B**

The presence of patent coronary artery bypass grafts is a potential hazard to reoperative surgery, but inadvertent injury to the grafts can be minimized by careful preoperative planning and intra-operative care. Pulmonary hypertension and an elevated CVP are common in patients with advanced heart failure and do not significantly impact decision making for this patient. Historically, poor ventricular function was associated with prohibitive risk for correction of mitral regurgitation, as repair or replacement removes the low resistance regurgitant pathway and might worsen heart function. However, the safety and potential benefits of mitral valve repair (or replacement with preservation of all subvalvular apparatus) in this setting are becoming convincing. Increasing emphasis is being placed on ventricular indices other than ejection fraction to predict patient outcomes following correction of mitral regurgitation in the setting of advanced heart failure. A recent review of outcomes in patients undergoing combined CABG and mitral valve annuloplasty for ischemic MR suggests that a preoperative left ventricular end-diastolic diameter (LVEDD) >6.5 cm is associated with reduced reverse remodeling and elevated early and late postoperative mortality. Similarly, a left ventricular end-systolic volume index (LVESVI) >150 mL/m^2 predicts the same bad outcomes. Reconsidering patient candidacy for surgery with these threshold values rather than ejection fraction can provide symptomatic benefit to many patients. Additional experience is required to determine the optimal combined management plan to improve mortality in this difficult population.

51. **Answer: E**

Cardiac resynchronization therapy (CRT or biventricular pacing) is an important tool in the management of systolic congestive heart failure. The concept is that with simultaneous pacing of right and left ventricles, contraction is better coordinated and ejection is improved. The timing of the right and left ventricular contractions can be adjusted to optimize "resynchronized" contraction. Several clinical trials demonstrated clinical improvement when selected patients with systolic ventricular dysfunction and heart failure were treated with CRT. Inclusion criteria included cardiomyopathy (ischemic or nonischemic), NYHA functional class III or IV despite maximal medical therapy (but not on continuous IV therapy), left ventricular ejection fraction ≤35%, QRS duration ≥120 ms (bundle branch block), and sinus rhythm. Using these "standard" selection criteria 60–70% of patients benefited symptomatically from biventricular pacing. Further studies have been completed outside these guidelines for patients in atrial fibrillation. Studies on heart failure patients with chronic atrial fibrillation are immature, but functional benefit from biventricular pacing is less impressive than for patients in sinus rhythm. In the examples given, atrial fibrillation is a relative exclusion without additional information. Patients on chronic inotropes were not candidates for the CRT trials, and there is no evidence that this level of end stage heart failure will benefit from CRT. Conversely, a patient with an EF of 40% likely has diastolic heart failure from hypertension and conventional medical therapy is indicated. Third degree heart block is an indication for A-V sequential pacing, but a narrow QRS complex is outside indications for biventricular pacing—a normal A-V pacemaker is sufficient.

52. **Answer: A**

Catheterization hemodynamics in pericardial constriction reveal three key features: (1) elevation and equalization of diastolic pressures in each of the cardiac chambers; (2) early diastolic "dip-and-plateau" or "square root-sign" configurations in the right and left ventricular tracings; and (3) a prominent y-descent in the right atrial pressure tracing. The constrictive effect of the thickened pericardium results in elevated, equalized diastolic pressures all cardiac chambers. Early diastolic filling is unimpeded and elevated venous pressures lead to abnormally rapid filling, while ventricular pressure decreases during this time. This rapid early diastolic filling then abruptly stops and ventricular pressure increases abruptly as intracardiac volumes approach the volume limit set by the noncompliant, thickened pericardium. The dip-and-plateau pattern (a.k.a. square root sign) of the ventricular waveform reflects rapid filling and arrested volume accumulation respectively. Equalized cardiac diastolic pressures and volumes translate to limited stroke volume and cardiac output. Increased sensitivity and specificity of hemodynamic testing can be augmented by provocative maneuvers. Intracardiac pressure dissociation is a phenomenon whereby inspiration leads to increased RV inflow and intraventricular septal shifting to the left, which reduce left ventricular filling. This creates a preload mismatch between the left and right sides of the heart, with elevated preload on the right compared to the left. Simultaneous right- and left-sided ventricular pressure tracings become discordant and begin to separate as a consequence, with LV pressures falling while RV pressures increase. The opposite occurs during expiration. This discordant response does not occur with restrictive disorders or congestive heart failure. Examination of the right atrial wave forms shows an exaggerated and deep y-descent compared to the x-descent, forming a characteristic M or W configuration. This is in contrast to cardiac tamponade in which the y-descent is attenuated or up sloping. Cardiac tamponade is the result of generalized cardiac compression throughout diastole. As such the diastolic surge that is seen in a constrictive pericardial patient is absent. Atrial filling occurs during ventricular ejection in early systole and the venous pressure tracing shows an absent or blunted diastolic y-descent.

53. **Answer: E**

Right ventricular wall thickness increases in response to volume and pressure overload, but in normal patients the normal range is 2.5 ± 0.5 mm. Normal pericardium is $\leq$2.0 mm thick. Pericardial resection for constrictive pericarditis can be fraught with technical difficulties. Dense adhesions between pericardium and epicardium develop, which can obscure identification of proper tissue planes. Common causes of pericarditis include past surgery, irradiation, past myocardial infarction, and infection. Consequently pericardial thickness is increased, the epicardium may not be identifiable, and the underlying myocardium may also be inflamed and friable. Significant raw-surface bleeding should be anticipated during the course of dissection, but a sudden rush of dark blood over the right heart suggests right ventricular entry. Attempts at primary repair in a flooded field that is incompletely mobilized may tear and avulse additional tissue and worsen the injury. In the described situation initiation of cardiopulmonary bypass is warranted to achieve a decompressed, bloodless field in which to identify optimal dissection planes, repair the laceration, and complete the pericardial resection. Abandoning the procedure may be appropriate if bypass is not available, but only complete pericardiectomy will resolve the patient's symptoms.

54. **Answer: D**

The chest film shows a globular heart shadow with minimal widening of the upper mediastinum. The echocardiogram shows a large posteroinferior pericardial effusion with compression of the right-sided (anterior) heart structures. The right ventricle is very small and compressed, which is opposite the expected findings for right heart strain from massive pulmonary embolism. There is no evidence of pericardial constriction. Although no color Doppler flow images of aortic valve function are shown, the large pericardial effusion dominates the findings and tamponade explains the clinical presentation. The fluid is most likely the result of breakdown of pericardial clot and osmotic volume expansion rather than pericarditis. Late cardiac tamponade is defined as tamponade occurring more than 7 days after cardiac surgery. This complication occurs in less than 1% of patients following cardiac operations, and this relative infrequency can delay diagnosis and treatment. It develops more common in women and in patients taking warfarin and/or antiplatelet medications. Patients can present with rapidly worsening dyspnea on exertion and exercise intolerance that can progress to hypotension. The best treatment is immediate admission and reoperation or catheter drainage to decompress the pericardial space. Opening the inferior aspect of the sternotomy to place a drain will rapidly resolve this condition.

55. **Answer: E**

This patient's ECG shows sinus tachycardia, but there are no acute injury patterns. Cardiac tamponade after surgery is a potentially lethal complication if not diagnosed and treated in a timely manner. The diagnosis is based on complete clinical assessment. This patient initially had excellent hemodynamic parameters, but initial brisk bleeding was documented. A significant drop in cardiac output associated with a new vasopressor requirement is alarming. Postoperative fluid resuscitation is commonly required, but this patient's elevated central venous pressure suggests that hypovolemia is not the cause of current low output. Acute graft closure would result in infarction or ischemia and consequent congestive heart failure, but the ECG shows only sinus tachycardia and nonspecific ST changes. A follow-up chest film would probably show a widened mediastinal silhouette, but this finding is nonspecific. A precordial echocardiogram would likely show clot or fluid (blood) collection, but a delay might be introduced and the quality of the study might be poor. In this setting the blood pressure and cardiac output changes are due to cardiac tamponade until proven otherwise. Clinical and hemodynamic findings are often atypical, the echocardiographic findings are clear in only about 60% of cases, and the risk of re-exploration is minimal. This patient should be returned to the operating room immediately for evacuation of retained blood and clot.

56. **Answer: E**

The figure shows a small pericardial effusion posteriorly and around the right atrium in addition to lung parenchymal infiltrates and volume loss in both lower lobes. In routine thoracic imaging, multifocal aneurysms, unexplained cardiomyopathy, and venous thrombosis in high-risk patients should suggest the possibility of AIDS. The incidence of pericardial effusions in HIV-infected patients is estimated at about 5%, but most are small and asymptomatic. In this population effusions can be manifestations of many infectious causes, although no single pathogen predominates. Malignancy is responsible for some effusions, but most often no cause can be identified and progression to symptoms is uncommon. Several older studies demonstrated shortened survival of AIDS patients once a pericardial effusion was diagnosed, suggesting a more advanced stage of the disease. HAART (highly active anti-retroviral therapy), which includes protease and nucleoside reverse-transcriptase inhibitors, was introduced in the mid-1990s. HAART therapy has evolved with variable composition, but it has no known therapeutic role for pericardial disease. The effects of wide use of these regimens on the incidence of effusive pericardial disease are not known, but effusions remain associated with advanced HIV infection. In the absence of symptoms pericardial drainage is not indicated.

57. **Answer: D**

A CT-guided biopsy of the lung mass can establish a diagnosis of the nodule, but no additional staging information is gained. Documentation of a malignant pericardial effusion or intrapericardial metastasis confirms stage IV disease, which defines definitive chemotherapy as indicated treatment. The most common malignancies that involve the pericardium are lung cancer, breast cancer, malignant melanoma, lymphoma and leukemia. Chylous pericardial effusions are rare, but they may be seen with extensive mediastinal disease from lymphoma, leukemia or small cell carcinoma. Malignant pericardial effusion often presents with tamponade, but true constriction is rarely caused by metastatic disease. Pericardiocentesis is an appropriate first therapeutic maneuver and cytology samples may confirm malignancy. Approximately 40% of malignant effusion taps, however, are non-diagnostic and the effusion recurrence rate is high. Pericardial biopsy doubles the diagnostic accuracy and improves drainage. The simplest access is the subxiphoid approach. VATS pericardial window is an excellent option for patients with simultaneous pericardial and pleural effusions, and biopsies of each space can be done either by thoracotomy or VATS. These approaches are associated with more pain than catheter drainage or subxiphoid window. Percutaneous balloon pericardiotomy can also create a pleural-pericardial communication. This procedure has been shown to be safe and effective for pericardial drainage, but biopsy is not possible and the pleural space fluid must then be addressed. Formal pericardiectomy is prudent only for documented pericardial constrictive disease, which features minimal pleural fluid and characteristic findings on CT, echo and right heart catheterization.

58. **Answer: E**

Asymptomatic pericardial effusion with pericarditis is a common finding during the acute phase of radiation-induced pericardial disease. Delayed pericarditis with or without effusion may present months to years following radiation therapy. Effusive-constrictive pericarditis should be considered in patients who present with a pericardial effusion and thickened pericardium. These patients typically present 1–4 years after radiation therapy with tamponade-like symptoms. Drainage fails to relieve symptoms because residual constrictive physiology persists. Right heart catheterization with pressure tracing analysis is the most sensitive and selective diagnostic test. Conservative or expectant care will provide no improvement. Diuresis will probably worsen symptoms. A CT scan or exercise testing will confirm abnormalities but no novel therapeutic suggestions are likely to result. When effusive-constrictive disease is identified pericardiectomy should be performed promptly.

59. **Answer: E**

The chest CT shows a “saddle” pulmonary embolus with bilateral clot. Obstruction to blood flow and cytokines induce pulmonary vasoconstriction, which leads to marked acute changes in right heart afterload. The right heart, a thin walled and relatively weak muscle compared to the left ventricle, is incapable of acute compensation. The RV distends, and secondary dilation of the tricuspid annulus in the anterior-posterior region results in tricuspid valve regurgitation (TR). TR exacerbates the right heart’s efficiency and further decreases forward cardiac output, leaving the left heart underfilled. Matching of ventilation and perfusion is grossly abnormal, and the aggregate abnormalities result in hypoxia, respiratory distress, and hypotension. This patient likely had a smaller PE a few days earlier and when preload was decreased by nitroglycerine he became hypotensive and was misdiagnosed with cardiac ischemia.

The treatment of pulmonary embolism is evolving. While smaller emboli may be treated with heparinization, massive PE as in this case carries a grave prognosis. While lytic therapy is an option for this patient, the risk of severe bleeding is high. Pulmonary embolectomy has been shown to lower this mortality compared to traditional therapy. John Gibbon first conceptualized the heart lung machine after watching a patient die from an attempted pulmonary embolectomy (the Trendelenburg procedure) by Dr. Edward Churchill at the Massachusetts General Hospital. While the first successful operation performed on the heart lung machine was for an atrial septal defect (Thomas Jefferson University, 1953), the quest for better treatment of massive pulmonary embolism led to the machine’s genesis.

60. **Answer: D**

The haemodynamic distinction between organic and functional tricuspid regurgitation can be difficult. Generally, if the patient with severe tricuspid regurgitation has a right ventricular systolic pressure above 60 mmHg, then the tricuspid regurgitation is functional and the result of left-sided heart failure. However, if the right ventricular systolic pressure is 40 mmHg, there is a substantial organic component. The pressure tracings show mild pulmonary hypertension (PA systolic = 45 mmHg) and a right atrial v-wave spike to 23 mmHg) documents severe tricuspid regurgitation. Organic tricuspid disease is suspected, but this does not explain the complaint of shortness of breath. Rheumatic disease affecting both mitral and tricuspid valves is a likely explanation. Both pathologies should be addressed, but mitral repair for rheumatic disease is not predictably durable. Of the choices offered and because of her age, replacement of both A-V valves with bioprostheses is best.

61. **Answer: C**

Midgut carcinoid tumors may secrete 5-hydroxytryptamine (serotonin), tachykinins, and prostaglandins. The liver effectively inactivates these compounds from the portal circulation, but when disease advances to include hepatic or distant metastases the vasoactive substances produced are able to reach the systemic circulation. Clinically, this is characterized by flushing, diarrhea, and bronchospasm. It is believed that these same substances induce fibrous tissue plaques on the endocardial surfaces of the heart, predominantly on the right side (15% have left side involvement). Typical tricuspid involvement includes thickened and fused commissures and chordae tendineae. Similarly, tricuspid and pulmonary valve leaflets are thickened and retracted, resulting in combined stenosis and regurgitation. Up to 70% of patients with carcinoid syndrome have evidence of carcinoid heart disease with peripheral signs of right heart failure.

When symptoms are severe or if right ventricular dysfunction is demonstrated, valve replacement offers marked improvement and a possible survival benefit. Repair of such complex involvement, however, is unreliable. Previous reports favored use of mechanical prostheses because of potential early failure of bioprostheses from carcinoid plaque formation. However, the use of warfarin in the face of liver dysfunction poses an elevated bleeding risk and some patients will undergo subsequent hepatic resection, hepatic artery embolization or other surgery. Treating symptoms with somatostatin analogues (octreotide) seems to minimize plaque formation on tissue valves, and placing a bioprosthesis eliminates the risk of mechanical valve thrombosis. Although no large comparative series of different valve types is available, the use of tissue valves for carcinoid heart disease is presently favored.

62. **Answer: C**

Current guidelines for treating tricuspid regurgitation include:

Class I:

Severe TR in patients with MV disease requiring MV surgery (level of evidence B)

Class IIa:

1. Tricuspid valve replacement or annuloplasty is reasonable for severe primary TR when symptomatic (level of evidence C)
2. Tricuspid valve replacement is reasonable for severe TR secondary to diseased/abnormal tricuspid valve leaflets not amenable to annuloplasty or repair. (Level of Evidence C)

Class IIb:

Tricuspid annuloplasty may be considered for less than severe TR in patients undergoing MV surgery when there is pulmonary hypertension or tricuspid annular dilatation (Level of Evidence C)

Class III:

1. Tricuspid valve replacement or annuloplasty is not indicated in asymptomatic patients with TR whose pulmonary artery systolic pressure is less than 60 mmHg in the presence of a normal MV. (Level of Evidence C)
2. Tricuspid valve replacement or annuloplasty is not indicated in patients with mild primary TR (Level of Evidence C)

The described patient has peripheral edema and pulmonary hypertension, so a repair is the best option. The treatment of tricuspid regurgitation is in evolution. Dreyfus and colleagues performed a prospective study in over 300 patients to determine if early repair for tricuspid dilatation alone would lead to long-term benefits. Nearly half the patients who did not receive a repair had TR increases of two grades or more over a 12 year follow-up period. Only 2% of patients who underwent repair had similar progression of TR. Other studies have implicated persistent TR as an independent risk factor for worse mid-term outcomes after cardiac surgery. Despite this and other emerging evidence, the guidelines are limited, as listed above. With information from additional clinical studies, repair of the tricuspid likely will be more frequently indicated.

63. **Answer: C**

The signs and symptoms of tricuspid regurgitation and stenosis overlap. However, there are distinct characteristics of each. Tricuspid regurgitation (TR) is often due to left-sided heart failure and evolves with symptoms of fatigue and weakness that result from reduced cardiac output. Right-sided heart failure leads to ascites, congestive hepatosplenomegaly, a pulsatile liver, pleural effusions, and peripheral edema. In the late stages, these patients are wasted with cachexia, cyanosis and jaundice. Impressive jugular venous distention with an s-wave or fused c- and v-waves, followed by a prominent y-descent, is present. During inspiration, this finding is accentuated because of the physiologic increase in venous return. Not surprisingly, atrial fibrillation is common. Auscultation of the heart is notable for an S3 that increases with inspiration and decreases with a Valsalva maneuver, an increased P2 if pulmonary hypertension has developed, and a parasternal pansystolic murmur that increases with inspiration. The chest radiograph demonstrates cardiomegaly, increased size of the right atrium and ventricle, a prominent azygos vein, possible pleural effusion and upward diaphragmatic displacement owing to ascites. Tricuspid stenosis (TS) is most commonly rheumatic. It is rare to have isolated tricuspid stenosis, as some degree of TR is always present and coexisting mitral and aortic disease are occasionally seen. The incidence of rheumatic tricuspid valve disease in underdeveloped countries is still significant. Patients with TS also have presenting symptoms of fatigue and weakness related to reduced cardiac output. This lesion is more common in young women. A diastolic gradient across the valve causes the right atrium to thicken and dilate, while the right ventricle remains relatively normal in size, but underfilled. However, the clinical picture, similar to pure TR, features jugular venous distention, ascites, pleural effusions and peripheral edema. In sinus rhythm, the right atrial tracing and jugular venous pulse have prominent a-waves that accentuate with inspiration. The cardiac murmur is mid-diastolic and increases with inspiration. There may be an opening snap that is best heard along the left sternal border. The chest radiograph shows cardiomegaly with accentuated right atrial and pulmonary artery profiles.

64. **Answer: E**

Tricuspid valve excision is possible if pulmonary pressures are not elevated and the degree of infection is extensive. Blood flows passively through the right side of the heart to the lungs. After excision, approximately one-half of the patients report ankle edema and mild exercise intolerance. Early death occurs in 12% of drug addicts after excision without replacement of the tricuspid valve. Hemodynamic and functional statuses begin to progressively deteriorate after 5 years. Late survival in such patients is 63% at 15 years, with death due to return to drug addiction and not to recurrent right-sided endocarditis. After eradication of the infection, valve replacement can be performed months to years later. Although it is preferable to wait until patients have conquered their drug dependence prior to valve replacement, at times a one-stage procedure is required. Many techniques have been described, including partial excision, prosthetic replacement, and replacement with homograft tissue or a stentless porcine valve, but no technique has proven to be superior. The main principal of treatment is the same for all endocarditis, which is complete elimination of infection.

65. **Answer: A**

Treatment of the left side (mitral) pathology alone may result in improvement of pulmonary hypertension and tricuspid regurgitation, but at least 16% of patients with 1+ or worse tricuspid regurgitation (TR) progress and require intervention. Unfortunately, reoperative mortality approximates 35% in this group. Tricuspid repair can be done by several methods, including the DeVega suture annuloplasty, the Kay "bicuspidization" (plication of the posterior leaflet), or placement of flexible or rigid rings that may be partial, complete or near-complete. With each of these options sutures placed near the AV node and bundle of His should be avoided because of the risk of complete heart block.

A review of 790 patients treated at the Cleveland Clinic assessed durability and risk factors for failure of tricuspid repair. The authors reported that regurgitation remained stable over time with a rigid ring, increased slowly over time with a flexible band and rose rapidly over time with a DeVega suture annuloplasty and pericardial strip reinforcement procedures. Although indications and techniques for tricuspid repair are in evolution, limited data support repair with a rigid near-complete ring.

66. **Answer: B**

The advantages of mitral valve repair over replacement should dominate decision making about patients with mitral regurgitation, and every effort should be made to repair the tricuspid valve when indicated. Since there is no overwhelming advantage to either mechanical or bioprosthetic valves in the tricuspid position, patient specific factors need to be considered. Some of these include age, expected survival, arrhythmias, need for right ventricular access (biopsy post-transplant, hemodynamic monitors in CHF, need for pacemaker), status of liver function (for future anticoagulation) and contraindications to anticoagulation. In this case, severe right heart failure is obvious but tricuspid repair is not possible. A mechanical valve would commit the patient to long-term anticoagulation. A bioprosthetic valve would be a better choice for this patient or even a younger one, especially if the patient is a woman of a child-bearing age. No survival benefit (approximately 60% actuarial survival at 5 years) or difference in freedom from reoperation (>90% at 5 years) has been demonstrated for either mechanical or bioprosthetic valves in the tricuspid position. Because of the relatively low pressure of the right side, bioprosthetic valves are more durable in the tricuspid position as compared to the mitral. Freedom from structural degeneration is nearly 100% at 9 years, but non-structural dysfunction is high (73%) due to pannus formation on the ventricular side of the cusps. This remains a concern that needs further investigation.

However, prosthetic tricuspid replacement is not complication-free, and mortality approximates 10%. The risk of complete heart block is approximately 6%. Ten percent of patients require a pacemaker during hospitalization for tricuspid valve replacement, and up to 25% of patients need a pacemaker within 10 years. When tricuspid annuloplasty is done, the conduction system should not be at risk and the need for permanent pacing is less than 3%. Thrombosis of prosthetic tricuspid valves occurs at a rate of 1% per patient-year. Thrombosis was more common with past mechanical prostheses (Smeloff-Cutter, Bjork-Shiley) than with current bileaflet valves. Bioprosthetic valve thrombosis is rare. If a tricuspid prosthesis does clot, however, thrombolytic therapy has a reported success rate of over 80%. Despite the possibility of valve thrombosis, significant thromboembolic events are rare. Pulmonary embolization rates following tricuspid replacement has been reported to be less than 1%.

67. **Answer: E**

The ECG shows inferior ST depression (II, III, aVF) consistent with ischaemia. Right coronary artery (RCA) insufficiency after aortic root replacement occurs in 2–3% of cases and has been related to female gender, obesity, and a small LV outflow tract. Because of differences in porcine and human anatomy, malalignment of the RCA can occur and may not be observed until the RV is filled or distended after emergence from CPB. Coronary insufficiency is not unique to root replacement and can occur after any procedure involving the aortic valve. An early decision to perform RCA grafting in patients with poor RV function, inferior LV wall motion abnormalities or significant unexplained arrhythmias is usually life-saving. While these conditions can also be caused by other factors such as coronary air emboli, poor myocardial protection, or reactions to protamine and/or transfusions, these etiologies should be uncommon, transient, and encountered early while still in the operating room.

68. **Answer: C**

Coronary ostial obstruction by the supra-annular skirt of a prosthesis can be catastrophic, but the timing of this scenario and lack of anginal complaints suggests another cause. This patient's clinical situation and data are highly suggestive of "delayed" cardiac tamponade. In the immediate postoperative setting with invasive monitoring and chest tubes, tamponade is a primary concern, but days later it can be difficult to identify. The described patient is in marginally-compensated cardiogenic shock. Similar to the physiology of subdural hematoma, clot breakdown and unrecovered blood cause osmotic volume expansion in the pericardial space with insidious worsening of hemodynamics. Delayed tamponade can occur after traditional full sternotomy. When partial sternotomy is chosen the pericardium is not widely open and may not communicate with the pleural spaces, so this complication can develop with a smaller volume of postoperative blood loss. Tamponade is more common after valve surgery than CABG operations and it is more common in patients treated with anticoagulants. Aggressive fluid administration is the best immediate management, and the added preload will usually improve blood pressure and cardiac output enough to allow for emergent intervention. Diuresis is an incorrect strategy. A chest radiograph may show mediastinal widening and CT may show an effusion, but the functional information from an echo study is a better guide to treatment. In this case (see media) the echo shows a modest-size effusion in the first clip (subcostal four-chamber view), but the right parasternal view is more concerning for impaired atrial filling and moderate tamponade. Optimal resolution of this patient's crisis involves decompression by reopening all or part of the sternotomy with controlled anesthesia in the operating room. However, percutaneous placement of a pericardial drain may be effective if the effusion is large and accessible. If the patient is *in extremis*, then he should be fully skin-prepped and draped for bedside decompression under local anesthesia. This reduces the risk of hemodynamic collapse on anesthetic induction due to vasodilation and loss of preload. A thoracoscopic pericardial window is not appropriate in an unstable patient.

69. **Answer: A**

Stroke occurs in 1–5% of patients following cardiac surgery, and it can be a devastating complication. Most perioperative strokes occur in a delayed fashion after an initial period of normal neurologic function. This complication can be selectively treated with catheter-directed, intra-arterial administration of thrombolytic drugs within 6 h of the event, and clinical improvement is possible (38% in one series from the Cleveland Clinic). Treatment with thrombolytics intravenously is associated with a higher risk of bleeding in postoperative patients and is generally contraindicated within 14 days of major surgery. In non-surgical stroke patients, intravenous thrombolytics should be given within 90–180 min of stroke detection. An alternate plan is catheter-directed, intra-arterial thrombolytic infusion, which may be given within 6 h. Treatment outside these windows can lead to hemorrhagic cerebral complications. It is most likely that the described patient experienced an intraoperative embolic event. Treatment with thrombolytic therapy, whether intravenous or direct intra-arterial, is not recommended at 8 h, as efficacy is low beyond 6 h, and the risk of bleeding is extreme. Induced moderate hypertension and anticoagulation to arrest a propagating site of embolic clot are part of current guidelines for care. The described scenario is not consistent with pulmonary emboli or diffuse anoxic encephalopathy, so venous imaging studies and hyperbaric oxygen therapy are not appropriate considerations.

70. **Answer: E**

The echocardiogram illustrates discrete subvalvular aortic stenosis. This variety of subaortic stenosis can consist of a fibrous ridge localized to one segment of the left ventricular outlet or it can be circumferential. There may be associated aortic regurgitation due to aortic leaflet thickening; this is thought to result from the jet of blood produced by ejection through the stenoric subvalvular segment. Operation for discrete subaortic stenosis consists of complete transaortic resection of the fibrous ridge, often in conjunction with a septal myomectomy. There are other more severe forms of subvalvular stenosis that result in a "tunnel" type of left ventricular outlet obstruction, often with associated hypoplasia of the aortic annulus. These patients may be managed by an aortoventriculoplasty (Konno procedure) or a modified Ross procedure that enlarges the left ventricular outlet. The aortic valve itself is usually tricuspid without leaflet fusion; thus there is no role for aortic valvotomy or balloon dilatation. Continued follow-up is appropriate because the associated aortic valve regurgitation is likely to progress.

71. **Answer: D**

Williams syndrome is the association of supravalvular aortic stenosis, "elfin" facies, and mental retardation. Supravalvular stenosis is usually localized, often with an associated ridge inside the aorta, although in some cases it may be more diffuse. True stenosis of the aortic valve itself is rare in Williams syndrome. Thus, operations that involve the aortic valve are not generally applicable in this condition. Since continued growth of the aorta is desired, operations that involve circumferential graft replacement of the ascending aorta are also not appropriate. Patch enlargement of the aorta is most commonly used to repair this type of stenosis. Balloon dilation of the aortic valve will not address the aortic pathology.

72. **Answer: C**

Embryologically, the coronary sinus is an extension of the left superior vena cava. It lies in the atrioventricular groove behind the left atrium. When there is a defect in its roof, coronary sinus blood can enter the left atrium directly. Thus, a coronary sinus septal defect ("unroofed coronary sinus") in association with a persistent left superior vena cava can result in significant flow of systemic venous blood to the left atrium; this may produce systemic arterial desaturation when an atrial septal defect is closed. Anomalous hepatic venous drainage can cause a small right-to-left shunt into the left atrium; this is unlikely to cause significant systemic arterial desaturation. Unrecognized anomalous pulmonary venous drainage results in a persistent left-to-right shunt which does not produce systemic arterial desaturation. Pulmonary valve stenosis, even when severe, will not produce a right-to-left shunt when the atrial septum has been rendered intact. Ventricular septal defects produce left-to-right shunts except in cases of advanced pulmonary vascular disease (Eisenmenger syndrome) where increased pulmonary vascular resistance can produce a right-to-left shunt.

73. **Answer: D**

Anomalous origin of the left coronary artery from the pulmonary artery does create a left-to-right shunt which empties into the pulmonary artery. However, this shunt flow is usually small and in addition, this anomaly is rarely associated with complete atrioventricular septal defect. Azygos continuation of the inferior vena cava is a condition in which the inferior vena cava does not drain normally into the right atrium with the hepatic veins, but rather with the azygos vein into the superior vena cava. This would not cause an excessive amount of blood streaming from the left atrium; rather it would cause an excessive amount of blood streaming from the superior vena caval orifice if the tourniquet around the superior vena cava was cephalad to the entrance of the azygous vein. The most common partial anomalous pulmonary venous connection is drainage of the right superior pulmonary vein into the right superior vena cava. This is evidenced by excessive blood streaming from the superior vena caval orifice and not from the left atrium. A patent ductus arteriosus is commonly associated with complete arrioventricular septal defect. In some series this association is present in one of every three patients. The blood from the patent ductus arteriosus fills the pulmonary artery, traverses the pulmonary bed, and flows back to the left atrium, and becomes evident as an excessive amount of blood streaming from the left atrium. This should be the first consideration in the clinical setting described. A patent left superior vena cava to the coronary sinus would be evidenced by blood streaming from the orifice of the coronary sinus and not from the left atrium.

74. **Answer: B**

The three major technical challenges associated with total repair of complete atrioventricular (AV) septal defects are (1) complete obliteration of intracardiac shunts, (2) reconstruction of competent yet non-stenotic left and right AV valves, and (3) preservation of an intact conduction system. Large residual intracardiac shunts at either atrial or ventricular level are rare following repair. Small residual intracardiac shunts are usually well tolerated. Poor long-term results should not occur because of elevated pulmonary vascular resistance if patients are appropriately selected preoperatively. Left ventricular outflow tract obstruction is a known complication of an incorrectly placed patch used to obliterate the interventricular communication. Obstruction may also occur in some patients for anatomic reasons. Left ventricular outflow tract obstruction, however, causes hemodynamic deterioration early after repair. This complication is not well tolerated and it is thus not a cause of long-term problems. Creation of a competent yet non-stenotic left AV valve ("mitral" valve) can pose a real challenge in the small infant. Mitral valve regurgitation must be suspected in any patient with persistent hemodynamic deterioration after repair of complete AV septal defect, especially in the presence of normal sinus rhythm and absence of residual left-to-right shunts.

75. **Answer: C**

Atrial arrhythmias are uncommon following an arterial switch operation. Stenosis of the coronary artery origins has been extremely uncommon. The most common late complication after an arterial switch operation for transposition of the great arteries (TGA) is supravalvular pulmonary artery stenosis. Recanalization of the ductus arteriosus cannot occur since most arterial switch operations involve the Lecompte maneuver which requires that the ductus arteriosus be divided in order to transfer the bifurcation of the pulmonary artery to a position anterior to the ascending aorta. Stenosis at the aortic anastomosis is infrequent.

76. **Answer: B**

Atrial septal defects created by balloon septostomy are unlikely to close and it is, therefore, unlikely that the patients would develop lethal hypoxemia. The major reason for performing the arterial switch operation within the first 2 weeks of life for patients with transposition of the great arteries (TGA) and intact ventricular septum is to take advantage of the fact that the left ventricle in utero has increased wall thickness because the ductus arteriosus is open and the left ventricle pumps against systemic resistance. Left ventricular wall thickness decreases rapidly within the first weeks of life and several series have identified age older than 2 weeks at the time of operation as a risk factor for the arterial switch operation for TGA with intact ventricular septum. It is true that the newborn is well prepared physiologically to withstand the stress of an operation, in general, but this is not the dominant reason for performing an arterial switch operation in the first 2 weeks of life. The pulmonary vascular resistance is unlikely to be significantly elevated after an uncomplicated arterial switch operation for TGA, as most patients have essentially normal pulmonary artery pressures in the early postoperative period. Prolonged administration of prostaglandins may have deleterious effects, but some patients have been safely maintained on prostaglandins for many weeks.

77. **Answer: D**

In a patient with tricuspid atresia and a ventricular septal defect a Fontan-type operation is the future long-term goal. Closure of an atrial septal defect would be fatal because the only pathway for systemic venous return to the systemic ventricle would be removed. Closure of the ventricular septal defect would induce severe cyanosis by completely obstructing the main source of pulmonary blood flow. Since a Fontan-type operation requires the pulmonary vascular resistance to be low, a secure and properly placed pulmonary artery band will protect the pulmonary vascular bed while controlling congestive heart failure symptoms. The augmentation of pulmonary blood flow by a systemic-to-pulmonary shunt (Blalock-Taussig shunt) would be unnecessary and harmful as it would further risk the development of both congestive heart failure and pulmonary vascular disease.

78. **Answer: C**

A vascular ring should be suspected in infants with stridor, “wheezing”, recurrent respiratory tract infections, and the classic “seal bark” cough. It is important that the evaluation proceed in a step-wise fashion and that redundant testing not be performed once the diagnosis has been established. Angiography is rarely indicated for the diagnosis of a vascular ring. It is indicated if associated congenital heart lesions are to be simultaneously evaluated. The best initial diagnostic study is an antero-posterior and lateral chest X-ray. A barium swallow should be the next study. Deep, persistent, extrinsic indentation of the posterior aspect of the esophagus indicates either a double aortic arch or right aortic arch with retroesophageal left subclavian artery and left ligamentum. Persistent bilateral compressions of the esophagus on the antero-posterior view are usually present with a double aortic arch. Computed tomography and magnetic resonance imaging will in many cases demonstrate the precise morphology of a vascular ring. However, they are not good initial diagnostic studies because of the cost and low yield when applied to a large number of patients with stridor and no other evidence for vascular ring. They are typically used only if enough information is not obtained from the barium swallow to recommend vascular ring division through a left thoracotomy.

79. **Answer: D**

The diagnosis of ventricular septal defect (VSD) is usually made on the basis of clinical examination and history. Further diagnostic evaluation is aimed primarily at determining size, location, and number of septal defects. Associated complications of the defect including valve function, magnitude and direction of shunt, and pulmonary vascular resistance are also identified by additional studies. Echocardiography has replaced cardiac catheterization and cineangiography as a reliable and noninvasive method of obtaining most of the information required prior to surgical therapy. Two-dimensional echocardiography and color Doppler flow studies can reliably demonstrate size, number, and location of the septal defects relative to other intracardiac structures including the cardiac valves. Additional information regarding atrioventricular valve function and prolapse of aortic valve leaflets can also be demonstrated. Coronary artery anatomy, particularly of the proximal branches, can often be obtained by echocardiography but cineangiography is definitive. Preoperative knowledge of the course of the coronaries is not routinely required for surgical repair of isolated VSDs since a ventriculotomy is rarely necessary. Pulmonary artery pressure and pulmonary vascular resistance can be estimated by echocardiographic measurements of the peak flow velocity across the tricuspid valve if regurgitation is present. However, in cases where no tricuspid insufficiency is present or when elevated pulmonary vascular resistance is suspected, cardiac catheterization remains the most accurate method of assessment. In a 2 year old child with a VSD, cardiac catheterization is useful to determine pulmonary vascular resistance and response to therapy such as oxygen or nitric oxide.

80. **Answer: E**

At cardiac catheterization oxygen saturation and pressures are recorded in each great vessel and cardiac chamber. When there is an increase in oxygen saturation from the superior vena cava (SVC) to the pulmonary artery (PA) there is a left to right shunt present, the chamber at which the O_2 step-up first appears disclosing the level of the defect. If there is an oxygen stepdown between the left atrium and aorta, a right to left shunt is present. The magnitude of a left-to-right shunt can be calculated from oxygen saturation data. Using the Fick principle the pulmonary blood flow

$$\mathrm{Qp} = \frac{\mathrm{O_2\ \ Uptake}}{\mathrm{Pulmonary\ vein\,O_2\ \ content} - \mathrm{pulmonary\ \ artery\,O_2\ \ content}}$$

and the systemic blood flow,

$$\mathrm{Qs} = \frac{\mathrm{O_2\ \ consumption}}{\mathrm{Aortic\,O_2\ \ content} - \mathrm{SVC\ \ O_2\ \ content}}$$

O_2 content is directly proportional to O_2 saturation, thus the latter can be substituted in these equations. Also, O_2 uptake equals O_2 consumption. Thus, when the first equation is divided by the second,

$$\frac{\mathrm{Qp}}{\mathrm{Qs}} = \frac{\mathrm{Aortic\ saturation} - \mathrm{SVC\,saturation}}{\mathrm{PV\,saturation} - \mathrm{PA\,saturation}} = \frac{(100-55)}{(100-85)} = 3.0$$

This relationship, which can be estimated from easily measured data, is extremely useful in managing patients with congenital defects such as in determining the need for operation and in determining the balance of pulmonary and systemic blood flows in patients following such operations as the Norwood procedure.

81. **Answer: B**

After surgery for congenital heart disease, severe low cardiac output state may be refractory to maximal medical management. Mechanical circulatory support may allow salvage of many of these challenging patients. Three forms of mechanical support are currently available to infants and children: (1) the intra-aortic balloon pump (IABP); (2) the ventricular assist device (VAD); and (3) extracorporeal membrane oxygenation (ECMO). Each technique has advantages and disadvantages. This child has biventricular dysfunction, probably from stunned myocardium following a prolonged crossclamp and bypass time, and requires biventricular extracorporeal support. The criteria for extracorporeal support include significant ventricular dysfunction despite maximal inotropic support with no residual correctable defects and reversible ventricular dysfunction. The IABP is available in small sizes for use in neonates, but the aortic arch surgery performed in this patient represents a contraindication to IABP use. Three types of VAD may be utilized: left, right, and biventricular. Children with left ventricular dysfunction are even less likely than adults to have preserved right ventricular function and pulmonary function. Nevertheless, in cases of isolated left ventricular dysfunction, highly selective left ventricular assist devices have been utilized with eventual survival of 40–70%. Use of a VAD without an oxygenator via existing right atrial and aortic cannulas is not appropriate because deoxygenated blood would be pumped into the aorta. ECMO utilizes veno-arterial bypass with a membrane oxygenator, which allows both hemodynamic and pulmonary support. ECMO results have been excellent as treatment for neonatal respiratory failure. Reported survival exceeds 80% for some indications, including neonates with meconium aspiration, persistent fetal circulation, and primary pulmonary hypertension. ECMO has been utilized with increased frequency to provide postcardiotomy support for children with severe cardiopulmonary dysfunction after surgery for congenital heart disease. Myocardial recovery can be expected in some patients in 24–48 h, and most patients who are going to recover sufficiently to be weaned from ECMO will do so in 5–7 days. Survival for postcardiotomy application of ECMO after biventricular repair is approximately 40%, but it is less following single ventricle palliation. ECMO provides total cardiopulmonary support and may allow the heart and lungs to heal. Although this may be accomplished with venous drainage from the right atrium and inflow into the aorta, many centers feel it is important to decompress the left side of the heart as well with an additional drainage catheter in the left atrium. Although adult ECMO can be conducted via femoral vein and femoral artery, it is not possible to use the femoral vessels in a neonate because of their small sizes. Veno-venous ECMO is a useful technique for isolated respiratory dysfunction such as meconium aspiration, but it is not useful in patients with severe cardiac dysfunction.

82. **Answer: E**

Supraventricular arrhythmia is the most common late problem for patients after a Fontan procedure. This is particularly true for patients that have had an atriopulmonary type Fontan. These patients can develop massive right atrial dilation and their repairs often involve multiple atrial suture lines. These two factors contribute significantly to late atrial tachycardias. Patients with atrial arrhythmias and dilation of the atrial portion of the atrio-pulmonary connection benefit greatly from conversion to an extracardiac Fontan and right atrial maze procedure. Protein-losing enteropathy in Fontan patients is less common than supraventricular tachycardia. Most of the difficulties with pleural effusions occur in the early postoperative period and generally resolve with time. The incidence of pleural effusions seems to be reduced when the Fontan pathway is fenestrated. Congestive heart failure due to failure of the single ventricle is relatively uncommon.

83. **Answer: E**

Inserting a right ventricle-to-pulmonary artery conduit is necessary in the repair of many congenital heart defects to establish unobstructed blood flow between the right ventricle and the pulmonary circulation. This is often referred to as a "Rastelli" procedure. Whether reconstruction is achieved with a bioprosthetic valve-conduit or a homograft conduit, progressive stenosis and restriction to pulmonary blood flow often occurs after several years. Calcification plays a major role in the development of this stenosis, but calcification in and of itself is not an indication for conduit change. Although most of these patients develop pulmonary stenosis as their chief problem, some also develop pulmonary regurgitation. Indications for conduit replacement because of pulmonary regurgitation include exercise intolerance, atrial and/or ventricular arrhythmias and progressive ventricular dilation. Occasionally such patients can initially be treated with balloon valvuloplasty. More frequently, however, because of a combination of somatic growth and calcification of the valve leaflets the conduit requires replacement. Cath findings of a peak gradient greater than 50 mmHg or an echocardiographic mean gradient over 50 mmHg, near-systemic right ventricular pressures or severe tricuspid regurgitation are all indications for surgical intervention. The development of right ventricular hypertrophy alone does not justify conduit replacement.

84. **Answer: D**

Sinus of Valsalva aneurysms are uncommon lesions involving the aortic root sinuses. These lesions are characterized by thin-walled outpouchings of tissue arising from media-deficient regions of the aortic sinuses and extending to surrounding cardiac structures. Approximately 50% have an associated subarterial ventricular septal defect. They may remain asymptomatic for many years, but are prone to rupture with consequent fistulization to adjacent cardiac chambers or the pericardial space. While they may occur in any of the three aortic sinuses, the right (67%) and non-coronary (25%) sinuses are affected much more frequently than the left coronary sinus. The incidence of fistulas from the various sinuses and the percent distribution to adjacent cardiac structures are shown below:

Anatomy of Aneurysms or Fistulas of The Sinus of Valsalva (n = 149) in 129 Patients

Site of rupture	Right coronary sinus	Left coronary sinus	Noncoronary sinus	Total
Nonruptured	31	19	29	79
Ruptured				
Right ventricle	35	1	6	42
Right atrium	9	0	11	20
Left atrium	1	1	2	4
Left ventricle	2	0	1	3
Pericardium	0	0	1	1
Total	78	21	50	149

From: Takach TJ, Reul OJ, Duncan JM, et al. Sinus of valsalva aneuyrsm or fistula: management and outcome. Ann Thorac Surg 1999; 68: 1573–1577

Rupture of a sinus of Valsalva aneurysm from the non-coronary sinus results in a fistula to the right atrium in most patients. Likewise, a ruptured sinus of Valsalva aneurysm from the right coronary sinus fistulates into the right ventricle most frequently. Sinus of Valsalva aneurysms of the left coronary sinus are rare and may result in a fistula to the left atrium or the pericardial space. Presenting symptoms of rupture of a sinus of Valsalva aneurysm are those of aortic valve regurgitation and congestive heart failure. Patients diagnosed with a sinus of Valsalva aneurysm should undergo surgical repair to resect the aneurysm tissue and to close (with patches) the sinus defect and any associated ventricular septal defect. If aortic regurgitation has developed secondary to prolapse or elongation of the involved aortic leaflet, repair of the aortic valve may also be indicated. The approach is through a median sternotomy using cardiopulmonary bypass and cardioplegic arrest. The lesions can usually be exposed and repaired through the aortic root, although exposure may be improved by opening the involved cardiac chamber. In the illustration a noncoronary sinus of Valsalva aneurysm is visualized. Its "windsock" is inverted and excised to create an elliptical opening. The defect is closed transversely. Excellent surgical results are currently obtained in most patients with these lesions.

85. **Answer: C**

Several factors may increase the risk of the Fontan operation in patients with single ventricle physiology. The ideal candidate has: (1) low pulmonary artery pressures (systolic PA <15–18 mmHg); (2) pulmonary vascular resistance (PVR) <2 Woods units; (3) a low transpulmonary gradient <8 mmHg; (4) a competent atrioventricular valve; and (5) good systolic and diastolic ventricular function (ejection fraction >50%, LVEDP <10 mmHg). Pulmonary blood flow is passive and driven only by the difference between the central venous pressure and the pulmonary venous pressure. Therefore, obstruction due either to anatomic (narrowed pulmonary arteries or veins) or physiologic factors (PVR) will make a successful Fontan procedure less likely. In multivariate risk analyses, pulmonary artery pressure and pulmonary vascular resistance are highly linked variables. Anatomic abnormalities and variations such as bilateral superior vena cava or interrupted inferior vena cava may require additional technical modifications to achieve the Fontan reconstruction, but add no significant operative risk. Pulmonary artery stenosis, if surgically correctable, does not pose an increased risk for Fontan. Decreased ventricular systolic or diastolic function increases the risk of the Fontan procedure. An ejection fraction <40% or an LVEDP >12 mmHg are considered relative contraindications to the procedure. Likewise, pulmonary artery systolic pressure >20 mmHg, PVR >4 Wood units, or a transpulmonary gradient over 10 mmHg are each associated with increased risk for the Fontan procedure.

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